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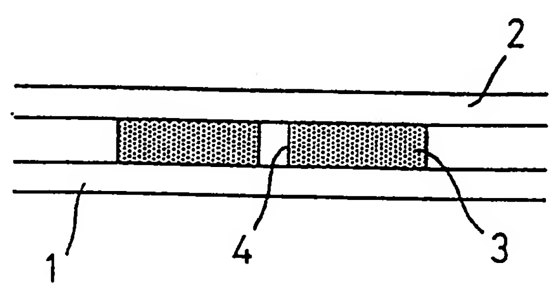

(57) Abstract

A microfluidic structure comprises first and second substantially planar form-stable base layers (1, 2), and an intermediate spacing layer (3) of elastic material, said spacing layer (3) being recessed to define a microcavity or channel system (4) with at least one of said first and second base layers. The structure is produced by moulding the spacing layer, optionally applied to or integral with a first base layer (2), against a planar mould, and the microcavity or channel system is completed by applying a second base layer (1), and optionally said first base layer (2), to the spacing layer (3).

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TITLE

MICROFLUIDIC STRUCTURE AND PROCESS FOR ITS MANUFACTURE

FIELD OF THE INVENTION

The present invention relates to an improved microfluidic structure which may find use in various fields of application such as various electrophoretic procedures, capillary chromatography, liquid distribution systems and the like, as well as to a process for the manufacture thereof.

BACKGROUND OF THE INVENTION

A recent development of electrophoretic technique is capillary electrophoresis. As with conventional methods of electrophoresis charged molecules may be isolated and determined in an electric field based upon their relative mobilities. A capillary electrophoretic system basically consists of a fused silica capillary having an inner diameter of approximately 25 to 100 microns and which connects two reservoirs filled with buffer. Separation takes place in the buffer filled capillary and substances may be detected by UV absorbance or emitted fluorescence by means of a concentrated transverse beam of light passing through the capillary.

In relation to conventional gel electrophoresis the use of a capillary system permits a considerably higher electric field strength due to reduced generation of heat and an improved cooling effect (reduced ratio of cross-sectional to circumferential area). This results in very fast separations with extremely high resolution.

Drawn glass capillary tubes have, however, several disadvantages. Among those may be mentioned the difficulty of providing branched systems as well as the difficulty of creating areas having particular surface characteristics. It is also relatively difficult to manufacture extremely small bore glass tubes. Further, glass capillaries are also unsuitable for parallel channel analyses and only small volumes can therefore be separated, separations for preparative purposes thereby being impractical.

To overcome these disadvantages planar structures have been developed in which a number of trenches or channels are fabricated in parallel. Typically, such a planar structure is produced by etching trenches in a semiconductor substrate, such as a silicon wafer, and then covering the etched surface by a cover plate to complete the electrophoretic channels. Such structures are, however, rather expensive to produce. Further, since the materials used are rigid and hard, it is difficult to provide an adequate sealing between the top edges of the etched trenches and the cover plate. As the etched substrate is most often a semiconductor, the material per se is unsuitable for electrophoretic applications and the channel side-walls must therefore be provided with an insulating surface layer, such as by oxidation or by coating with some other material.

SUMMARY OF THE INVENTION

An object of the present invention is to provide a microfluidic structure suitable for capillary electrophoresis and which is devoid of the above disadvantages and thus is relatively cheap to produce, optionally permitting a disposable type product, may provide branched flow channels, may exhibit local surface characteristics, and provides great freedom in choice of material, e.g. as regards surface, optical and electric properties.

Another object of the present invention is to provide a microfluidic structure which, in addition to capillary electrophoresis, is suitable for other applications such as capillary chromatography, procedures using micro reaction cavities, miniaturized liquid communication units etc.

Still another object of the present invention is to provide a microfluidic structure in the form of a multi-storey construction having channels or cavities in several planes to thereby permit the build-up of complex channel or cavity geometries for analyses or reactions.

Another object of the present invention is to provide a microfluidic structure which permits easy detection of substances in the flow system.

A further object of the present invention is to provide a process for the manufacture of the above microfluidic structure.

Thus, in one aspect the present invention relates to a microfluidic structure comprising first and second substantially planar base layers of a form-stable material, and an intermediate spacing layer of elastic material, said spacing layer being recessed to define a micro cavity or channel system with at least one of said first and second base layers.

In another aspect the present invention provides a process for the manufacture of such a microfluidic structure, which process comprises the steps of providing a mould having a planar face with a relief pattern corresponding to the desired spacing layer geometry, including said liquid flow system, applying and moulding a spacing layer material against the mould surface, optionally together or integral with a superposed first base layer, removing the mould from the shaped spacing layer, applying a second base layer to the shaped surface of the spacing layer to complete the liquid flow system therewith, and, if not done previously, applying said first base layer to the opposite surface of the spacing layer.

BRIEF DESCRIPTION OF THE DRAWINGS

The above objects, features and advantages will be apparent from the following description and the appended claims, taken in conjunction with the accompanying drawings, in which:

Fig. 1 is a plan view of an embodiment of a capillary electrophoretic plate according to the present invention;

Fig. 2 is a plan view of one of the base layers of the structure in Fig. 1 including detector and electric contact means;

Fig. 3 is a plan view of the other base layer of the structure in Fig. 1 supporting a spacing layer defining an upwardly open liquid channel;

Fig. 4 is a partial cross-sectional view of the structure in Fig. 1;

Fig. 5 is another embodiment of capillary electrophoretic plate according to the present invention;

Fig. 6 is a schematic illustration of the manufacture of a number of base layer/spacing layer assemblies corresponding to that in Fig. 3;

Fig. 7A is a schematic cross-sectional view of a sandwich structure comprising three superposed spacing layers with intermediate base layers, and Fig. 7B is a cross-sectional view of one base layer/spacing layer assembly used to build up the sandwich structure;

Fig. 8 is a partial cross-sectional view of a structure comprising integral spacing and base layers;

Fig. 9 is a partial cross-sectional view of the structure shown in Fig. 8 placed in a clamping means;

Fig. 10 is a schematic view of another embodiment of base layer including an ion exchanger strip; and

Fig. 11 is a diagram showing the result of an electrophoretic procedure performed with a capillary electrophoretic plate of the invention.

DETAILED DESCRIPTION OF THE INVENTION

In its simplest form the microfluidic structure according to the present invention consists of two base layers between which an elastic spacing material, which is firmly attached to at least one of the base layers, forms a geometric micro structure defining the desired liquid flow system, e.g. one or more cavities or a labyrinth-like channel.

For the provision of the liquid flow system the spacing layer may be recessed through a part or the whole thickness thereof. In the first case the spacing layer forms the side walls and one of the top and bottom walls of each cavity or channel, one of the base layers forming the other of the top and bottom walls, whereas in the latter

case the base layers form the top and bottom walls and the spacing layer forms the side walls. Due to the elasticity of the spacing layer adequate sealing thereof to the respective base layer(s) is obtained.

In a development thereof the structure of the invention consists of a "multi-storey" sandwich structure having two or more spacing layers separated by base layers, the liquid flow systems in adjacent spacing layers communicating by apertures or bores in the intermediate base layers. In this way e.g. complex flow channel systems may be formed. Such a multi-storey structure may be formed by piling several base layer/spacing layer assemblies on top of each other.

The base layers should be form-stable, which term, however, herein is to be understood in a relatively broad sense as will be further elucidated below. Therefore, not only non-elastic materials but also moderately elastomeric materials may be contemplated as will readily be appreciated when considering the below stated purpose of and requirements on the base layers. Thus, the purpose of the base layers is, on one hand, to support the spacing layer as well as to form part of the channel or cavity walls, and on the other hand to maintain and ensure the dimensions of the structure in the XY-plane thereof; the XY-plane is that of the base layer plane extension, and Z is the direction perpendicular thereto. Form-stable therefore refers to a material that will give only small and well defined dimensional changes under conditions dictated by the particular application. The base layer surface should have a good surface smoothness to ensure efficient sealing under moderate pressures. This may be implemented, for example, by the base layer being stiff or by using a flexible film placed on a planar and possibly elastic surface. As suitable materials for the base layer, which may be in plate, sheet, foil or film form, may be mentioned glass, metal or plastic, such as polyester, polyethylene terephthalate, e.g. Mylar, fluoroplastic, e.g. Hostaflon. The above mentioned apertures in the base layer,

necessary for e.g. sandwich applications, may be accomplished by high precision techniques such as laser drilling or numerically controlled precision machinery.

As mentioned above the purpose of the spacing layer is to build up the side walls of the channels or cavities and provide for the desired elasticity in the Z-direction , i.e. perpendicularly to the plane extension. The material should thus be elastic, i.e. preferably be a rubber or an elastomer. An example of a suitable type of material is silicone rubber. Other specific examples are EPDM rubber and Hostaflon. Depending upon the method used for the manufacture of the base layer/spacing layer assembly, which will be described in more detail below, the spacing layer material should also have satisfactory properties as a moulding material, such as low viscosity and form shrinkage, a suitable curing or hardening principle, e.g. UV-light or other radiation, temperature, etc, as well as a suitable hardness to provide for efficient sealing. The above properties makes it possible to transfer and multiply with great accuracy the exact geometry from precision-made moulds or dies to cheap polymeric materials. Such high precision moulds or dies may, for example, advantageously be fabricated by etching in single crystal materials, as will be described below. As mentioned previously, the elastic or resilient properties of the spacing layer or layers permit a very good sealing between base and spacing layers, or between adjacent spacing layers, to be obtained. The spacing layer (when stabilized) should preferably also have surface properties providing for suitable surface characteristics when joined to a base layer and defining a cavity or channel therewith, e.g. hydrophobic-hydrophobic interaction for applications involving aqueous solutions.

Concerning the basic structure of the invention consisting of two base layers and an intermediate spacing layer, it is readily realized, however, that there are materials that will satisfy at the same time the requirements on both the base layer and the spacing layer. The spacing layer and one or both of the base layers may

then be made of the same material. In such a case the spacing layer and one base layer may also be integral as will be further described below. The above described multi-storey structure may, of course, also be made up from such integral base layer/spacing layer units. An example of a material that may be used in this respect is Hostaflon.

Preferably, the spacing layer does not fill the whole space enclosed by the two base layers, but only to the extent to provide for sufficient wall thicknesses of the channels or cavities defined thereby. Thus, for e.g. a winding channel the spacing layer material defining it will exhibit the same winding geometry but with a wider cross-section. In this way inter alia a smaller sealing area is obtained, thereby requiring a lower total sealing force to be applied for a given surface pressure.

The elasticity of the spacing layer(s) may also be used to give the structure the function of a pump or valve by variation of a force acting in the Z-direction, i.e. normally to the base and spacing layer planes. The force required to compress the structure to obtain such a pumping action will also be lower the more reduced the spacing layer extension is, as just discussed above.

As stated hereinbefore the required recessing of the spacing layer is, in accordance with the invention, accomplished by forming the spacing layer against a planar mould, e.g. a sheet or plate, which has a moulding surface provided with a relief pattern being the negative of the desired geometric structure to be exhibited by the spacing layer. Such a mould may, for instance, be produced by etching, surface coating, laser processing, electrochemical etching, mechanical processing, or combinations thereof, of a substrate of, for instance, silicon, quartz, ceramic, metal or plastic material, e.g. PMMA or Teflon®. The mould used for forming the spacing layer may, of course, very well be a replica of an originally manufactured master mould produced therefrom by casting or moulding.

The preferred method of producing such a mould involves etching. The material of choice is then a single

crystalline material, like e.g. silicon or quartz, or various group III/V materials, such as e.g. gallium arsenide, i.e. a material which has such a structure/composition that a well-defined surface will be produced by chemical processing in gas or liquid phase, and which has such mechanical/thermal properties that it will withstand the pressures and temperatures required by such forming process. A preferred material is single crystalline silicon.

The etching of a desired relief pattern on the surface may be effected in a manner known per se, i.e. by providing the substrate with an etch stopper layer (usually by oxidation), coating with a photosensitive layer (photoresist), exposing the surface through a mask defining the desired relief pattern, and developing the exposed areas to remove the photoresist therefrom, and then opening the bared etch stopper layer in those areas, removing the remaining photoresist mask, and finally etching the bared substrate surface areas to the desired depth.

The moulding of the spacing layer may be performed in various ways. Thus, for instance, in one embodiment the spacing layer is formed by a compression moulding type procedure, involving impression, or coining or embossing, of the spacing layer material. In this case the spacing layer material, optionally attached to or integral with a base layer, is applied against the mould surface, and the assembly is pressed together by an external force. In case the material is thermoplastic, the viscosity thereof is lowered by increasing the temperature, and the spacing layer relief pattern formed is then made permanent or stabilized by lowering the temperature. Other ways of stabilizing the spacing layer includes cross-linking thereof, e.g. by UV-radiation, a catalyst, heat, etc. In the latter case the spacing layer material may be a thin layer of a cross-linkable liquid, such as a silicone rubber, coated on the surface of the base layer.

In another embodiment the spacing layer is formed by an injection moulding type procedure. In this case the base

layer is applied against the mould surface, and the base layer and the mould are pressed together by an external force. A cross-linkable liquid, e.g. a silicone rubber, is then pressed into the mould cavity formed, whereupon it is cross-linked by appropriate cross-linking means, such as UV-light. Alternatively, a thermoplastic polymer melt might be injected to form the spacing layer when stabilized by cooling.

When the hardening or stabilization of the spacing layer is completed, the base layer/spacing layer assembly is removed from the mould. In order to facilitate the release of the formed spacing layer from the mould, the latter is preferably treated with a release agent prior to the moulding operation, e.g. a fluorotenside in liquid phase or a fluoropolymer in gaseous phase.

After removal from the mould the second base layer is applied to the spacing layer to complete the desired cavity or channel system. Optionally this second base layer is covalently or otherwise bound to the spacing layer by suitable means as will be discussed in more detail below.

In order to achieve optimum sealing between the spacing and base layers, the assembly thereof is, at the time of use for the particular application, placed in a clamping means between planar faced clamp members capable of exerting a compressive force on the assembly. Such a clamping means may also be used to make the assembly perform the above mentioned pumping action.

For electrophoretic purposes the second base layer is advantageously provided with contact means, e.g. gold strips, at each end thereof, as well as detector means or at least provisions therefor. In such a case this second base layer is preferably made reusable, whereas the first base layer with attached spacing layer is of disposable type and separable from the second base layer such that after use the latter may readily be provided with a new base layer/spacing layer assembly.

As mentioned above the microfluidic structure of the invention may, of course, advantageously also be designed

for other microfluidic purposes than electrophoresis. Among those are e.g. capillary chromatography, micro-reaction cavity procedures, miniaturized liquid communication units, biosensor flow cells, etc. Reaction cavities constructed in accordance with the invention may, for example, be used for various forms of solid phase synthesis, such as peptide or oligonucleotide synthesis, PCR, DNA-solid phase sequencing reactions, just to mention a few.

Fig. 1 illustrates a capillary electrophoretic plate according to the present invention. It consists of a first base layer 1, a second base layer 2, and an elastic spacing layer 3 disposed between the two base layers 1, 2. The spacing layer 3 is recessed to define a channel 4. For illustrative clarity only, the base layer 2 is here made transparent (Figs. 1 and 3).

The base layer 1 is made of a form-stable, i.e. non-elastic or moderately elastic, material, for instance glass, and is at each end portion thereof provided with electrode strips 5, 6, e.g. of gold film. In the illustrated case the base layer 1 is also provided with a conductivity detector means 7 in the form of a pair of e.g. gold electrodes 8, 9 arranged to cross the channel 4 and extending from contact pieces 10, 11, e.g. also of gold, on either side of the base layer.

The elastic spacing layer is attached to the second base layer 2, e.g. a polyester film, as shown in Fig. 3. In the illustrated case the spacing layer 3 is a labyrinth-like structure having the channel 4 recess therethrough. In Fig. 3 the spacing layer 3 is attached to the bottom side of the base layer 2, and the channel 4 is therefore open downwardly, whereas the top wall thereof is formed by base plate 2. The spacing layer 3 may, for example, be made of silicone rubber.

The capillary electrophoretic plate as shown in Fig. 1 is formed by applying the base layer/spacing layer assembly of Fig. 3 to the base layer 1. Due to the elasticity of spacing layer 3 efficient sealing against the base layer 1 is obtained. By matching the surface properties, the

importance of which has been mentioned above, sufficient adhesion between base layer 1 and spacing layer 3 for them to stick together will be obtained. For certain material combinations gluing may, however, be necessary.

In a specific non-limiting example, with particular reference to the electrophoretic plate in Fig. 1, the base layer is of glass and has a length of 60 mm, a width of 20 mm and a thickness of about 0.5 mm. The spacing layer 3 is made of silicone, General Electric 670 (General Electric Company), with a hardness of 90 shore and has a width of 1 mm. The length of channel 4 defined thereby is 100 mm and its width 250 microns. The channel depth, i.e. the thickness of the spacing layer, is 50 microns and the volume is 1.25 microlitres. The electrodes 8, 9, which may be of gold, have a width of 50 microns and a spacing of 50 microns. The base layer 2, which is of polyester, is 12 x 40 mm and has a thickness of about 0.2 mm.

To perform an electrophoretic separation with the capillary electrophoretic plate shown in Fig. 1 it is placed between two flat surfaces and an appropriate force is applied to hold the plate sandwich sealingly together. The channel 4 is filled with electrophoretic buffer by applying a liquid drop at one end and sucking it into the channel by means of vacuum. Sample is then applied to the channel, optionally by using the resilient structure as a pump or by an enriching ion exchanger zone as will be described below. Buffer soaked filter paper pieces, indicated in Fig. 1 with dashed lines and designated by reference numerals 12, 13, are applied to the respective ends of channel 4 to provide contact between the channel and the contact strips 5, 6, and the electrophoresis voltage from an external source is applied. The separation process is monitored by the detector 7.

Fig. 5 illustrates a variation of the capillary electrophoretic plate in Fig. 1. In this shown embodiment the channel 4 is closed at each end, and instead the channel opens into apertures 14, 15 made in the upper base layer 2a supporting the spacing layer. There are further no

contact strips on the lower base layer, here designated by reference numeral 1a. The buffer may be supplied by e.g. a respective small buffer filled container placed above each aperture 14, 15, into which containers electrodes are immersed for applying the external voltage field.

The spacing layer 3 may, for example, be produced by applying base layer 2 against a planar mould having a relief pattern corresponding to the labyrinth-like spacing layer structure including channel 4. The silicone material is then injected into the mould cavity and the spacing layer formed is subsequently cured by UV irradiation. After removal from the mould the spacing layer 3 supported by the base layer 2 is as shown in Fig. 3.

A schematic illustration of the production of a plurality of base layers 2 with attached spacing layers 3 as outlined above, e.g. of the materials and dimensions given hereinbefore as a specific example, is represented in Fig. 6. This figure is intended to illustrate a mould surface having a pattern of grooves 16 corresponding to seven spacing layers 3 arranged side by side.

A mould plate exhibiting the desired mould pattern may, for example, be produced as follows:

The surface of a silicon plate is oxidized in an oven at 1100 ^{o}C to form an oxide layer of a sufficient thickness, e.g. about 8000 Å. After washing, dehydration in an oven and priming with hexamethylsilane, a photoresist layer is applied by spinning and stabilized by baking. A mask corresponding to the desired groove pattern is then placed upon the plate surface, and the non-covered portions are subjected to light exposure. The exposed photoresist portions are removed by developer solution to bare the oxide layer, and the remaining photoresist mask is hard-baked. The bared oxide is then etched with hydrofluoric acid/ammonium fluoride to expose the silicon (the back-side of the plate being protected, such as by resistant tape) and the photoresist mask is removed by a suitable solvent, such as acetone. The oxide-free silicon areas are then etched by potassium hydroxide solution for a sufficient

time to produce the desired depth. The resulting mould surface will exhibit the desired pattern of grooves 16.

To produce the base layer/spacing layer unit 2, 3, a film or sheet of e.g. polyester (here represented as being transparent) is placed upon the mould surface, preferably after having treated the mould surface and film with a release agent. Pressure is then applied, e.g. 4 bars of compressed air, and a cross-linkable liquid, such as silicone rubber (e.g. RTV 670 supplied by General Electric Company) is introduced through the inlet 17 until it emerges at outlet 18. After photo-curing by UV light the base layer sheet is removed from the mould and cut into separate base layer sections (each forming a base layer 2) along lines 19, if not already done prior to application to the mould. Reference numeral 20 indicates transverse stop stripes (not shown in Fig. 1) to prevent buffer in filter papers 8, 9 in Fig. 1 from entering the structure beside the channel.

The structure shown in Fig. 3, consisting of base layer 2 and the spacing layer 3 supported thereby, may be used to build up multi-storey structures as is schematically illustrated in Fig. 7A showing three superposed spacing layer/base layer assemblies according to Fig. 7B. In such manner very complex channel geometries for reactions and analyses may be constructed. The channels of adjacent spacing layers 3 may be connected by bores in the respective base layers, the channel ends then being closed as in base layer 2a in Fig. 5.

In the electrophoretic plate shown in Figs. 1 and 5 the smaller base layer 2, 2a with attached spacing layer 3, which advantageously is of disposable type, may easily be torn off from the larger base layer 1 provided with detector means 7, whereupon a new base layer/spacing layer assembly 2, 3 may be applied to the base layer 1 which is the more expansive one of the two components.

With reference to the above described structure, and particularly to Fig. 4, the spacing layer 3 and one of the two base layers 1, 2 may be integral, i.e. produced as an

integral member from one and the same material. This is schematically illustrated in Fig. 8 wherein reference numeral 21 represents an integral base layer/spacing layer member defining a channel 22, and 23 indicates a second base layer.

The embodiment illustrated in Fig. 8 may e.g. be produced as follows:

A silicon mould plate having the desired relief pattern is first produced as described above, either for a single spacing layer or, preferably, for a plurality of spacing layers as in Fig. 6. A 300 - 500 μm Hostaflon film (Hostaflon is a thermoplastic fluoroelastomer supplied by Hoechst AG, Germany) is then applied to the silicon mould surface, optionally after applying a release agent, and a smooth silicon plate, i.e. without any relief pattern, is applied thereabove to sandwich the Hostaflon film between them. Gold coatings are then applied to the outer surfaces of the respective silicon plates. The sandwich is then placed in a pressing means, a pressure (10-50 kg/cm^2) is applied and the gold coatings are connected to a voltage source to electrically heat the sandwich to about 150^{o}C. Hereby the Hostaflon film softens and the mould surface pattern is impressed or coined into the plastic film. The voltage source is then disconnected, and the sandwich is allowed to cool. Upon removal from the mould, the resulting base layer/spacing layer unit has a cross-section corresponding to that schematically illustrated in Fig. 8, the spacing layer defining the channels having a thickness of about 50 μm. A non-coined Hostaflon film layer is then applied as the second base layer to complete the structure. This latter film has preferably been heat/pressure treated as above between flat silicon plates to provide a smooth contact surface. Optional liquid communication apertures (indicated as 14 in Fig. 5) are then drilled.

Fig. 9 illustrates the base layer/spacing layer unit 21, 22 of Fig. 8 inserted between clamping members 24, 25 to provide for efficient sealing between the components 21, 22 and 23, respectively. The upper clamping member 24

comprises a container recess 26 communicating with the spacing layer channel 22 through an aperture 27 for the introduction of a fluid into the channel, e.g. buffer in the case of an electrophoretic plate as outlined above in connection with Fig. 5.

It will be realized that in comparison with conventional capillary tube electrophoresis the electrophoretic plate according to the present invention offers several advantages. For example, it will be easy to provide branched inlets and outlets for the capillary structure, which in turn will permit such procedures as isotachophoretic concentration of the sample in a channel section at one end of the capillary channel structure, collection of fractions, and variation of connected electrolytes. Also preparative uses may be contemplated.

The electrophoretic plate having a capillary channel of rectangular cross-section as shown in the drawings and described above is further very advantageous from the viewpoint of detection. Thus, compared with conventional capillary tube electrophoresis it will be much easier to arrange various detector systems, one example being the conductivity detector mentioned above. Another example is the use of a UV detector. In that case the channel may be provided with one or more "windows", i.e. a UV transparent part of the channel bottom (in the illustrated cases base layer 1 or 1a). Such windows may be provided by e.g. metallizing a transparent base layer forming the bottom of the channel to leave a transparent opening or window at the desired site(s). Detection is then performed by illumination with a UV light source. By arranging a sequence of such windows at the inlet part of the channel the amount of sample injected may be determined. Optionally, detectors, such as UV detectors, may be arranged along the whole length of the channel, whereby the migration of the sample substance(s) in the channel may be monitored continuously. In an alternative arrangement a plurality of optical fibres opening towards the channel bottom may be used to direct the light to a detector array

for continuous monitoring of the whole or part of the channel. Other types of detectors are, of course, also possible. As is readily realized, the above described detection principles may also be of value for other applications than electrophoresis, such as e.g. chromatography.

Due to the resiliency of the spacing layer it will further be possible to provide for the injection of nanolitre quantity samples by a pumping action effected by varying the force that keeps the "sandwich" together. Also, the plate structure makes it possible to enrich sample molecules in an electrophoretic channel on a zone of e.g. an ion exchanger. An example of the provision of such an ion exchanger zone is given in Fig. 10 which illustrates an embodiment of a base layer corresponding to the base layer 1 in Figs. 1, 2 and 5. As shown in the figure, the base plate 28 has, in addition to detector electrodes 29, 30, a thin strip 31 of an ion exchanger material. When performing the electrophoresis with, for example, an electrophoretic plate according to Fig. 5, the strip 31 is within the channel 4, and sample in suitable buffer applied through the channel inlet is first enriched in ion exchanger strip 31. Electrophoretic buffer is thereupon introduced to remove the excess of sample in the channel 4. The sample is then desorbed by the electrophoretic field or the pH shift generated thereby.

Fig. 11 illustrates an electropherogram obtained in an electrophoresis of a restriction digest of ϕX174 with Hae III performed with a Hostaflon electrophoretic plate produced as described above by coining against an etched silicon surface. The total channel length was 50 mm, the channel width was 250 μm, and the channel height was 50 μm. In use the plate was clamped between the flat surfaces of a clamping means with a total force of about 100 N. The separation channel was hydrophilized with a non-ionic detergent and filled with 10% linear polyacrylamide as separation media and Tris-borate, pH 8.3, was used as buffer. Injection was electrokinetic at 5 sec/700 V, total

potential drop 700 V. Detection was performed by UV at 260 nm.

The invention is, of course, not restricted to the specific embodiments described above and shown in the drawings, but many modifications and variations are within the scope of the general inventive concept as stated in the appended claims.

CLAIMS

1. A microfluidic structure, characterized in that it comprises first and second substantially planar form-stable base layers (1, 2), and an intermediate spacing layer (3) of elastic material, said spacing layer (3) being recessed to define a micro cavity or channel system (4) with at least one of said first and second base layers.

2. The structure according to claim 1, characterized in that said spacing layer (3) is recessed through the thickness thereof such that the side walls of the cavity or channel system (4) are formed by the spacing layer (3) and the top and bottom walls thereof are formed by the base layers (1, 2).

3. The structure according to claim 1 or 2, characterized in that the spacing layer and at least one base layer are made of the same material.

4. The structure according to claim 3, characterized in that the spacing layer is integral with one of the base layers (21).

5. The structure according to any one of claims 1 to 4, characterized in that at least one of said base layers (1, 2) is flexible.

6. The structure according to any one of claims 1 to 5, characterized in that at least one of said base layers (1, 2) is rigid.

7. The structure according to any one of claims 1 to 6, characterized in that the spacing layer structure (3) does not fill the whole space between the base layers but only forms wall members of the channel or cavity (4) defined by the structure.

8. The structure according to any one of claims 1 to 7, characterized in that said structure is a plate for capillary electrophoresis.

9. The structure according to claim 8, characterized in that it comprises detector means (7) arranged on one of the base layers (1, 2).

10. The structure according to any one of claims 1 to 9, characterized in that said structure comprises at least two spacing layers (3) separated by base layers (1, 2), the channels or cavities of one spacing layer being connected to a channel or cavity of an adjacent layer by a bore in the intermediate base layer.

11. A process of producing a microfluidic structure, said structure comprising first and second substantially planar form-stable base layers (1, 2), and an intermediate spacing layer (3) of elastic material, said spacing layer (3) being recessed to define a micro cavity or channel system (4) with at least one of said first and second base layers, which process is characterized by the steps of (i) providing a planar mould surface having a relief pattern corresponding to the desired spacing layer geometry, the spacing layer material optionally being attached to or integral with the first base layer (2), (ii) moulding the spacing layer (3) against said mould surface, and (iii) after removal from the mould applying the second base layer (1), and optionally said first base layer (2), to opposite sides of the spacing layer (3) to complete the channel or cavity system (4) defined thereby.

12. The process according to claim 11, characterized by the steps of

a) providing a planar mould having a relief pattern corresponding to the desired spacing layer geometry;

b) applying a first base layer (2) against the mould;

c) injecting a cross-linkable polymer liquid or thermoplastic polymer melt into the cavity defined between the mould surface and the base layer (2);
d) stabilizing said injected polymer by cross-linking or temperature reduction;
e) removing the base layer/spacing layer assembly (2, 3) from the mould; and
f) applying a second base layer (1) to the spacing layer (3) of said assembly (2, 3) .

13. The process according to claim 11, characterized by the steps of
a) providing a planar mould having a relief pattern corresponding to the desired spacing layer geometry;
b) applying a cross-linkable or thermoplastic spacing layer material, optionally supported by or integral with a first base layer (2), against the mould and pressing the assembly together, optionally with heating;
c) stabilizing the spacing layer (3) formed by cross-linking or temperature reduction;
d) removing the spacing layer structure from the mould; and
e) applying a second base layer (1), and optionally said first base layer (1), to the spacing layer (3).

14. The process according to claim 13, characterized in that an integral base layer/spacing layer member is produced in steps b) and c).

15. The process according to any one of claims 12 to 14, characterized in that said cross-linking is effected by photo-initiation.

16. The process according to any one of claims 11 to 15, characterized in that said relief pattern of the mould surface is produced by etching.

17. The process according to claim 16, characterized in that said mould is made of single-crystalline silicon.

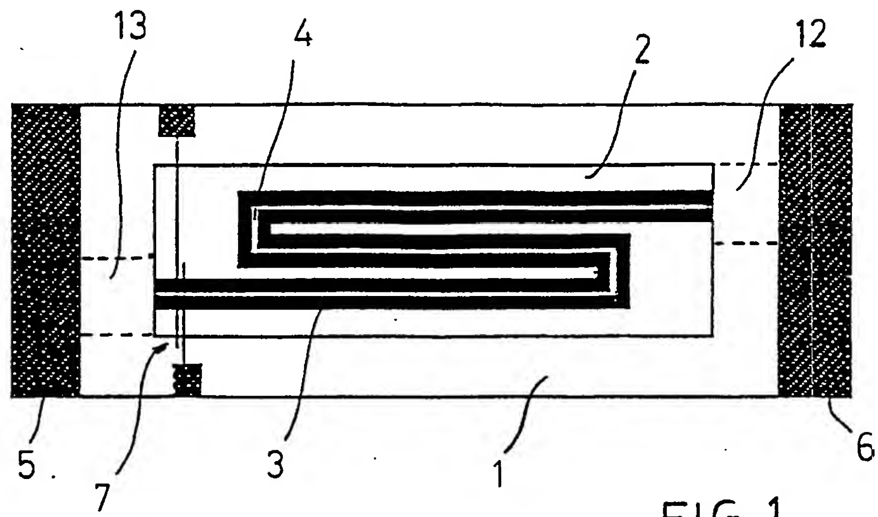

FIG. 1

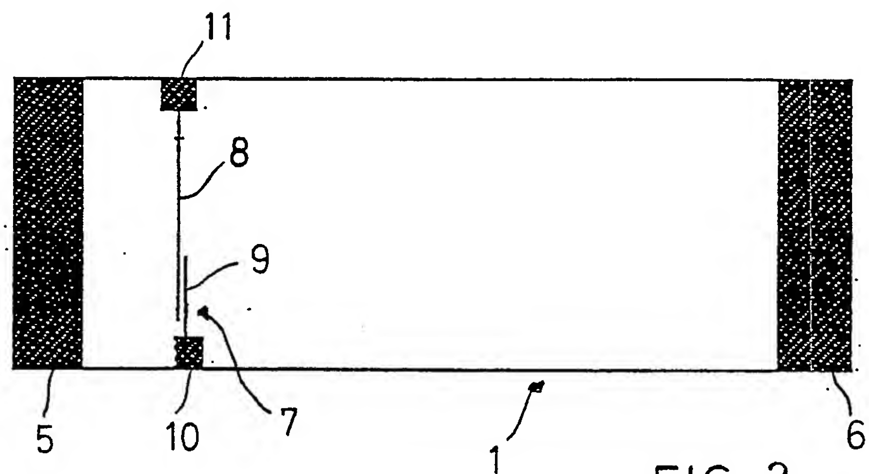

FIG. 2

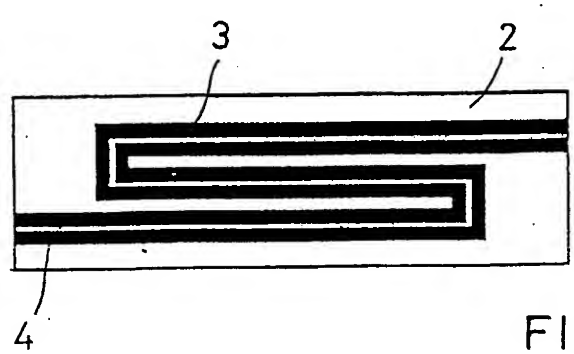

FIG. 3

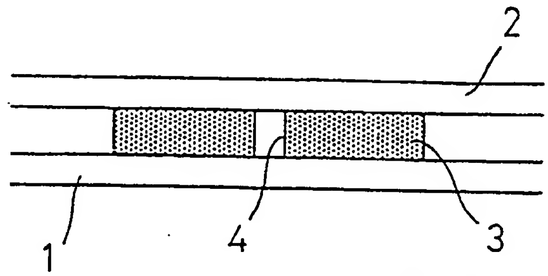

FIG. 4

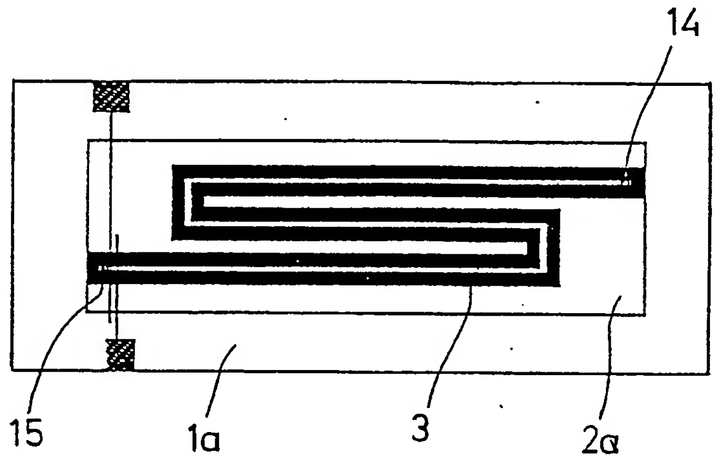

FIG. 5

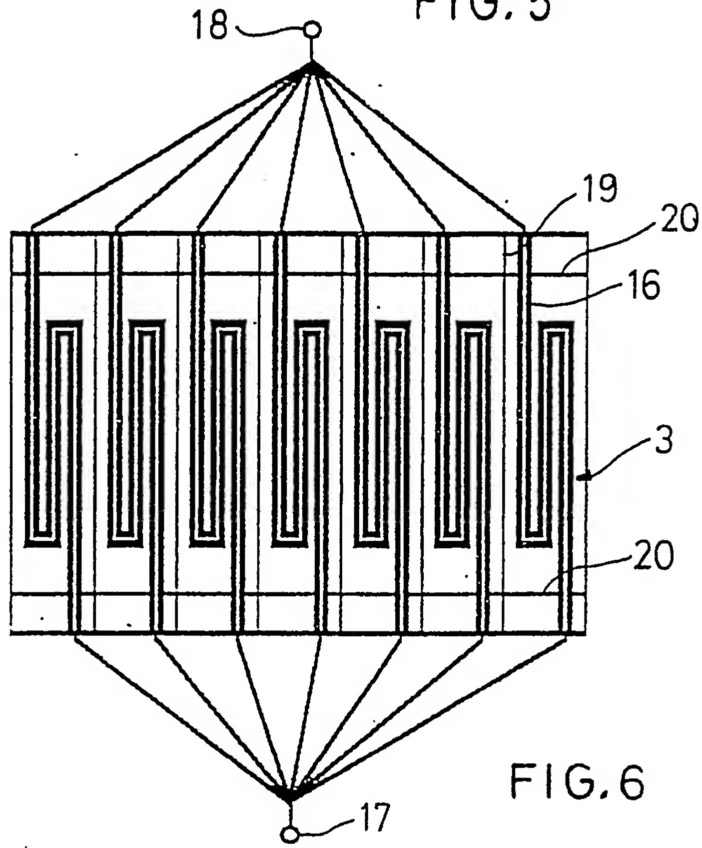

FIG. 6

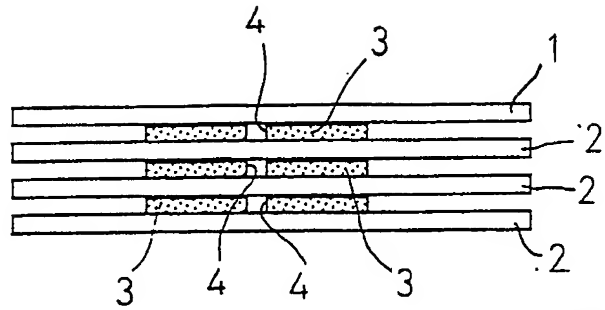

FIG. 7A

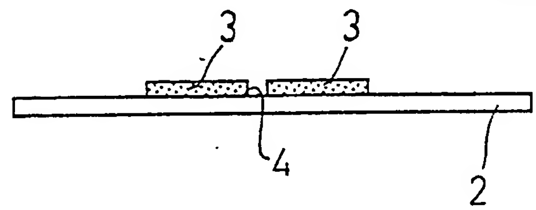

FIG. 7B

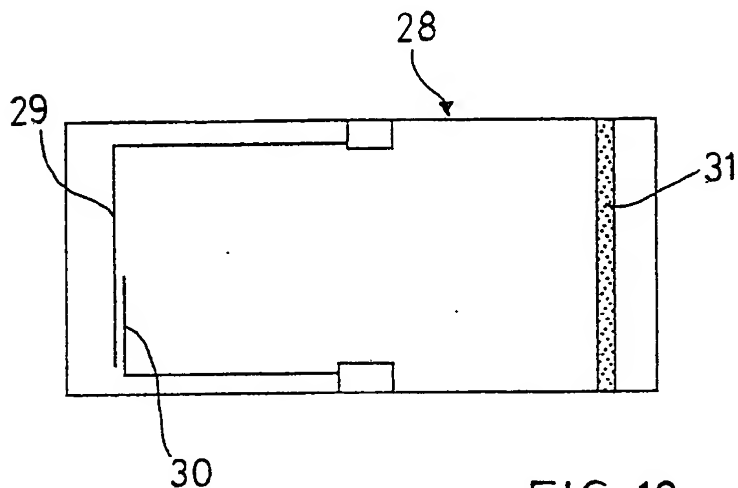

FIG. 10

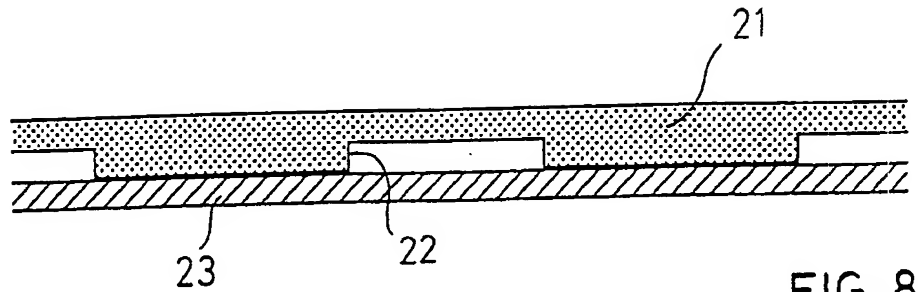

FIG. 8

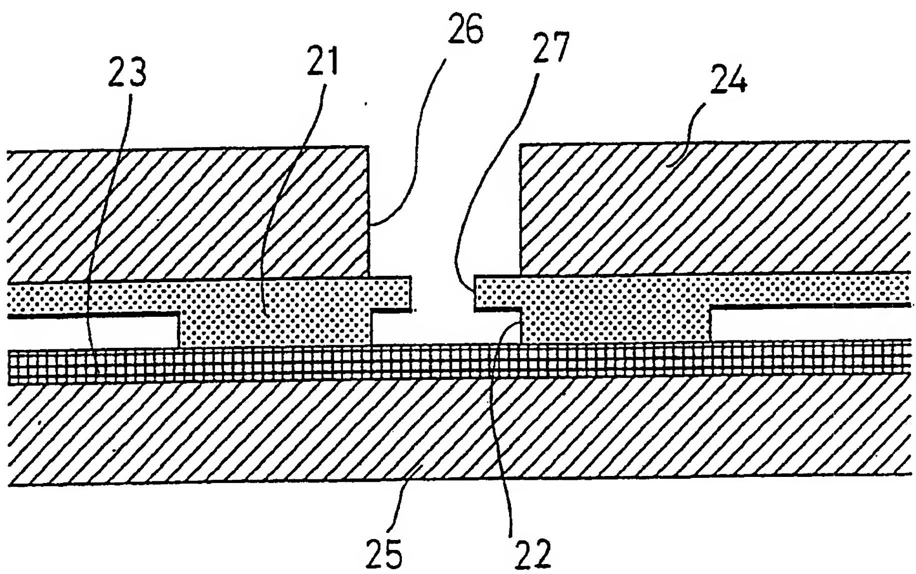

FIG. 9

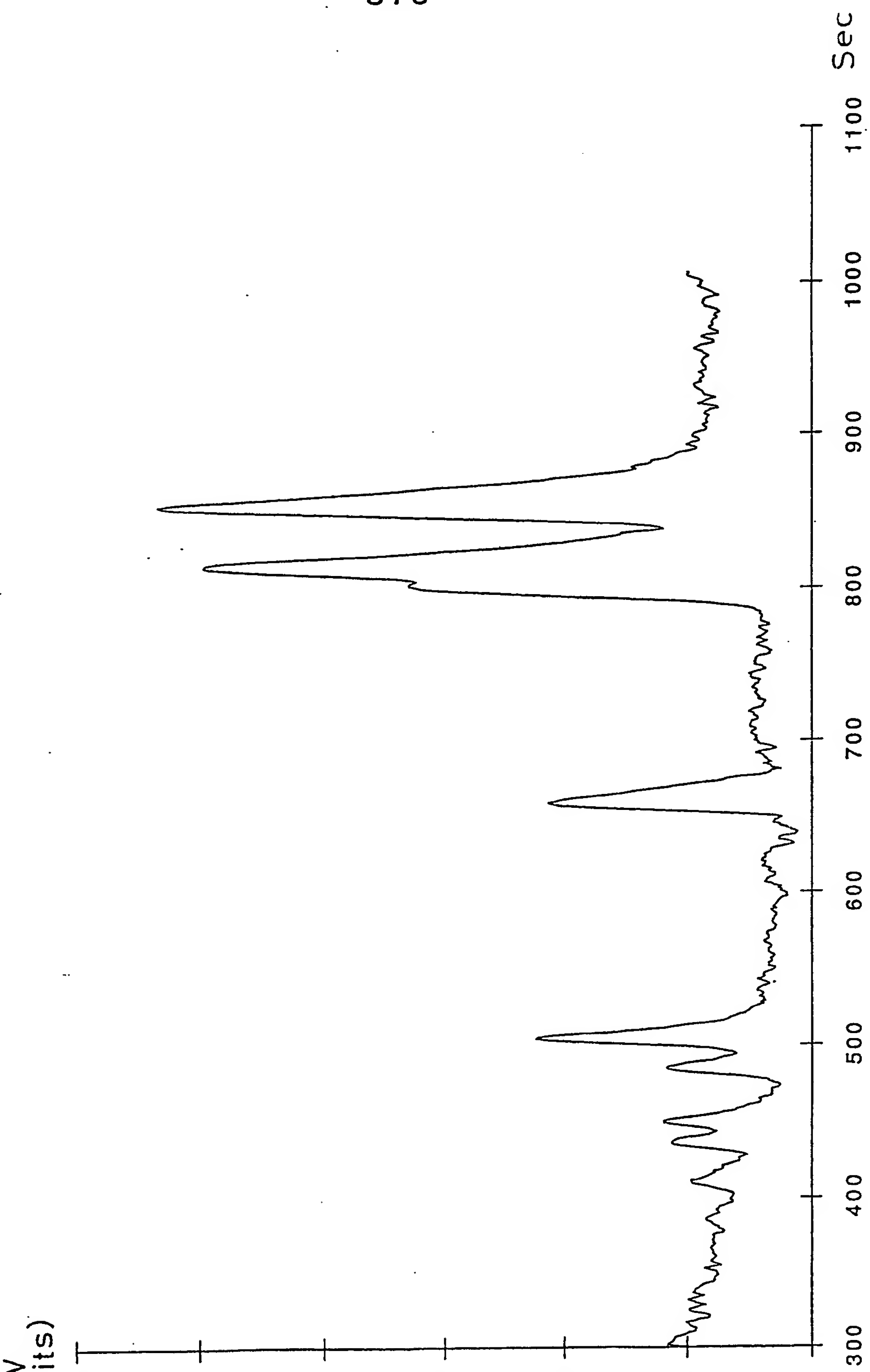
UV (units)
3000
2500
2000
1500
1000
500
0
300
400
500
600
700
800
900
1000
1100
Sec

FIG. 11

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 91/00327

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: B 01 D 57/02, G 01 N 27/26, B 01 L 3/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	G 01 N; B 01 L; B 01 D; B 29 C

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP, A1, 0010456 (EASTMAN KODAK COMPANY) 30 April 1980, see the whole document --	1-17
A	US, A, 4900663 (S.I. WIE ET AL) 13 February 1990, see figure 4 --	1-17
A	EP, A2, 0347579 (MESSERSCHMITT-BÖLKOW-BLOHM GESELLSCHAFT MIT BESCHRÄNKTER HAFTUNG) 27 December 1989, see page 3, column 4, line 3 - line 26; figure 6 --	1-17
A	EP, A2, 0107631 (BIFOK AB ET AL) 2 May 1984, see page 5, line 20 - page 6, line 6; figure 1 --	1-17

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
9th July 1991	1991 -07- 30
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Inger Löfgren

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.PCT/SE 91/00327

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the Swedish Patent Office EDP file on 91-05-29
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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		US-A-	4254083	81-03-03
		AT-T-	4249	83-08-15
		CA-A-	1119831	82-03-16
		CA-A-	1133059	82-10-05
		EP-A-B-	0010457	80-04-30
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		CH-A-B-	671[illegible]	89-08-31
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0313657.9 13 June 2003 (13.06.2003) GB

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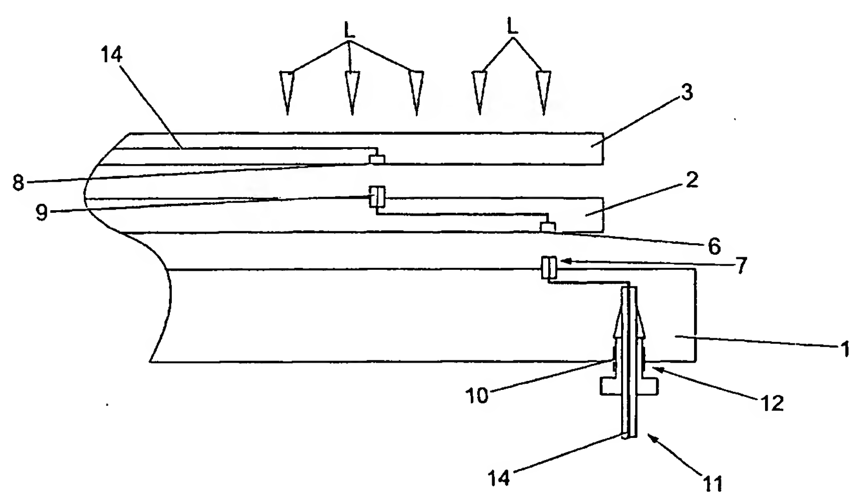
(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MODULAR MICROFLUIDIC SYSTEM



(57) Abstract: A modular microfluidic system is described having at least one base board with a plurality of fluidly linked fluid supply apertures, optional intermediate level boards of equivalent construction, a plurality of microfluidic modules adapted to be detachably attached to the base board/ intermediate boards, each having one or more fluid inlets and/or outlets, and a plurality of fluid couplings preferably in the form of projecting ferrules to effect releasable fluid connection between a module and a base board/ intermediate level board via a supply aperture on the board and an inlet/outlet on the module. A method of providing a microfluidic system as a modular assembly is also described.

WO 2004/022233 A1

MODULAR MICROFLUIDIC SYSTEM

The invention relates to a microfluidic system having a modular construction for rapid assembly and disassembly, and a method of providing such a system.

Microfluidic devices and systems have become increasingly important in recent years for performing large numbers of different chemical and/or biological operations on a manageable scale, since they allow a large number of chemical or biochemical reactions to be carried out as part of an analytical and/or synthetic process in a relatively small liquid volume. Such miniaturised analytical or synthetic operations are generally more efficient, producing increased response times and reduce the requirement for potentially expensive reagents.

Conventional microfluidic devices and components have been constructed on a chip using technology analogous to that followed in the silicon fabrication industry in general, for example by constructing the devices in a planar fashion using photolithography and etching techniques. Conventionally, there has been a tendency, in particular by analogy with miniaturisation elsewhere in the silicon industry, to concentrate development efforts on miniaturising onto a single chip of as small a size as possible all chemical, biochemical and biological processing associated with a particular synthetic and/or analytical process.

Such constructions offer many advantages. However, the resultant chip is relatively inflexible. It is not always easy to intermix different materials and device technologies within such a single chip. Inspection, maintenance and repair can be complex.

It is an object of the invention to provide a microfluidic system which offers enhanced flexibility and which mitigates some or all of the disadvantages of single chip integral systems.

It is a particular object of the present invention to provide a modular microfluidic system in which various different microfluidic components are readily assemblable and disassemblable into a complete system to offer enhanced flexibility and utility.

Thus, according to the present invention in a first aspect there is provided a modular microfluidic system comprising at least one base board having a plurality of fluidly linked fluid supply apertures on one or both sides thereof, a plurality of microfluidic modules adapted to be detachably attached to the base board, each having one or more fluid inlets and/or outlets, and a plurality of fluid couplings to effect releasable substantially fluid-tight fluid connection between a module and a base board via a supply aperture on the base board and an inlet/outlet on the module.

Preferably further the system comprises at least one fluid source aperture fluidly linked thereto to supply source fluid to the system, and/or at least one fluid output aperture fluidly linked thereto to output fluid from the system. Source and/or outlet apertures may be provided in direct communication to the baseboard or via modules. A plurality of such fluid source apertures and/or fluid output apertures may be provided.

The fluid supply may be gaseous or liquid. More than one fluid may be supplied to any given system.

In accordance with the invention, the microfluidic circuit is built up on the base board, with the system being formed in modular fashion upon the base board chip, rather than being integrated therewith in conventional manner. Fluid is supplied to the constructed microfluidic system via the fluid source aperture in the baseboard or by direct introduction into a module. The base board chip is preferably constructed with a pattern of at least partly interconnecting microfluidic channels to provide a plurality of fluid channels and/or chambers linking in fluid communication at least some of the supply apertures to each other and/or to the source aperture. The fluid supply passages within the modules act in co-operation therewith to complete a desired microfluidic circuit when the modular structure is assembled, the circuit serving to distribute fluid to interconnection points on the board and hence to the modules. The assembled system may provide a plurality of such circuits functioning in association or independently.

The invention offers significant advantages, particularly in relation to flexibility of construction in use, when compared with prior art systems. Chip module to base board interconnections may be made conveniently compact and simple, whilst at the same time connections between the board and external equipment can utilise well established fittings for interfacing to that equipment. Intermixing of different materials and device technology is enabled (for example glass chips on a polymer board). In the same way a choice of external systems such as external pumps as well as on-board or module-surface mounted pumps and valves etc. is offered.

The system of the invention offers flexibility of design choice. For example a simple baseboard design may be provided with exchangeable complex modules, or complex systems may be included within the baseboard, with the modules attachable thereto being simple and/or disposable. Seals and

connections between module and board can be selected according to module function.

The overall system provides for simple inspection and maintenance, flexibility of use, and ease of repair to systems, for example by replacing only a module which is defective rather than an entire system.

A microfluidic module in accordance with the invention comprises one or more microfluidic devices. As used herein, a microfluidic device may comprise any known element of a microfluidic system, including without limitation an active device unit, such as a reactor, heater, cooler, analyser, detector, mixer, processor, separator or the like, a fluid function unit such as a pump, valve, filter or the like or merely a fluid channel, chamber or manifold to complete a particular microfluidic circuit.

Microfluidic devices in accordance with the invention may be three dimensional or generally planar. In a preferred embodiment, the devices are generally planar. Each module has a generally planar construction to be incorporated upon a generally planar baseboard. Inlet/outlet apertures are most conveniently provided on one of the planar faces of such a module. Supply apertures are most conveniently provided on a planar face of the baseboard, and source aperture(s) may be provided at an edge or edge face or the same or opposite planar face thereof.

In particular, each module preferably has a generally planar sandwich construction, comprising at least one inner sandwich layer defining a fluid channel and/or chamber portion, and at least one cover layer covering and effecting enclosure of the same. In a preferred embodiment the module comprises at least one sandwich layer defining an enclosed fluid channel

and/or chamber portion, for example consisting of paired sandwich elements into the surface of at least one of which channels are created such that the pair assembled together define such an enclosure, with cover layers at either side thereof. Further intermediate layers may be present.

Active microfluidic elements may be incorporated within the channels and/or chambers so formed in the sandwich layer or additionally or alternatively may be provided upon the module surface in fluid communication with the channel therewithin. One or more inlet and/or outlet apertures are provided to effect a fluid communication between the channel and an external surface of the module, for fluid connection to the baseboard. A baseboard may be similarly constructed.

The base board and of the modules may be fabricated conveniently in suitable plastics material. They may be constructed from monolithic blocks of material, from sandwich layers as above described, or from thin layer laminates or combinations thereof. Layers or materials which contact fluid in use are preferably fabricated when necessary from chemically resistant plastics material, such as epoxy, a photoimagable epoxy being most preferred. Suitable resistant thin film laminate materials might include epoxy glued PEN laminates. This gives good resistance with good fabricability of fluid channels and chambers. In sandwich structures, cover layers including fluid inlet/outlet ports which might also contact fluid in use are also preferably fabricated from materials exhibiting good chemical resistance, for example epoxy or other plastics such as polyetheretherketone (PEEK). Alternatively, materials may be given a suitably resistant coating in such areas.

Chemical properties of merely structural cover or intermediate layers might be less critical. Likewise material selection might be less critical for components

intended for use with fluids presenting a less harsh environment. In these cases less resistant materials such as PMMA, PET, acrylic polymers and the like might be suitable.

Additionally, any materials or layers and in particular cover layers might also be modified for specific properties, for example for transparency, for electrical, magnetic or dielectric properties, to provide mountings for externally mounted microfluidic device components etc. Metallic layers may be provided or incorporated, for example to serve as a conductor, resistive heater or otherwise.

In practice, different parts of individual components might have different functional requirements, for example regarding transparency, structural strength, chemical resistance etc. Combinations of materials may be used, for example using a combination of materials and components and by using composite substrates for the baseboard and modules to achieve the best combination of properties.

For example, in the case of a microchemical reactor it is beneficial to use a substrate polymer that is optically transparent to enable easy inspection of the fluid path and/ or to allow measurements and/or is thermally transparent or transparent at other wavelengths for any purpose. It will be understood however that a readily available polymer with good transparency that is also resistant to a wide range of solvents used in synthetic chemistry is not generally available. By adopting a composite approach a substrate can be readily formed comprising a composite structure having areas of a transparent material (not necessarily exhibiting high chemical resistance) where required, and areas of a chemically resistant material (not necessarily exhibiting high transparency) at least in regions where solvent contact is possible, preventing

contact with the less resistant transparent substrate material. For example a basic structure comprises transparent material but in which inserts of chemically resistant material are included in the substrate in regions where solvent contact is possible. Alternatively a basic structure of chemically resistant material with "window" inserts of transparent material will serve the same purpose. Specific areas with other functionality will similarly readily suggest themselves.

As used herein, microfluidic will be understood to refer to microstructures having at least some sub-millimetre dimensions, microstructure in this case being used to refer to any of a variety of well known structures in such systems, including, but not limited to, the channels and chambers hereinabove described, that are capable of providing passage or storage for a fluid.

In accordance with the invention, a plurality of fluid couplings are provided to effect a fluid-tight connection between at least one fluid supply aperture on a base board and at least one inlet/outlet on a microfluidic device module. Fluid tight connection is preferably effected by interference fit between a coupling and a supply aperture, and couplings and apertures are sized and materials for their fabrication selected accordingly, for example being flexibly resilient at least in the region of connection.

This interference fit alone may be sufficient to maintain a fluid-tight connection, at least in use under action of supplied fluid pressure. Alternatively connecting means may be provided to hold the assembly together in use and assist in maintenance of a fluid-tight connection between modules and board by urging coupling and aperture into closer association and retaining thereat with a suitable urging force. Such connecting means may for example comprise spring clips, screws, bolts, clamps or like mechanical

fixings. The connecting means connect modules and board together. There is no need for specific connecting means separately associated with each coupling/ aperture connection. One or a few mechanical fasteners can be used to hold together a system making multiple fluid connections.

These connecting means will typically be releasable as it is a feature of the invention that modules are readily assembled into multiple configurations and are able to be dissasembled by a user for example for reassembly into other configurations. However it will be appreciated that in certain circumstances the user may wish to use more permanent fixings to retain coupling and aperture in fluid-tight association on a semi-permanent or permanent basis, for example by permanent mechanical fixing or gluing, and a system in accordance with the invention allows a user to choose to do this.

Conveniently, the connection comprises a releasable coupling, for example in the form of a channel means removably insertable into a suitable recess in such a inlet/outlet/aperture to effect a fluid tight communicating connection therebetween. Such channel means conveniently comprises a tubular element, in particular a rigid tubular element, for example being parallel sided, for example being square or rectangular, polygonal, or alternatively having a circular or elliptical cross section, with any recess into which such a tubular element is to be received preferably being shaped accordingly.

Such a tubular element can be a separable and distinct unit. However, for convenience, particularly in relation to the preferred embodiment where base board and module comprise generally planar components, the tubular element preferably comprises a projecting ferrule integral with and projecting from a first aperture comprising either a fluid supply aperture in the base board or an inlet/outlet in the module, and adapted to be received in a recess comprised as

a second aperture, correspondingly either an inlet/outlet in the module or a supply aperture in the base board. In particular the ferrule projects generally perpendicularly from a generally planar surface, to effect a fluid connection between a base board and module adapted to lie generally parallel when connected.

In a most preferred form, ferrules are provided which project above the surface of the base board to be received within recesses comprising the inlet/outlet apertures of modules to be attached thereto.

Ferrules as above described can offer particular advantages. The ferrule system enables dead volume in fluid path between "chips" to be minimised. Use of ferrules allows higher density of interconnections than other fittings such as high-pressure liquid chromatography (HPLC) fittings and the like. Ferrules can withstand high pressures. Ferrules generally require a reduced thickness of material in which to be held compared to the thickness needed to hold a screw thread or like fitting, allowing much thinner layers, down to layers essentially comprising films, to be interconnected. One or a few mechanical fasteners can be used to hold together a system making multiple fluid connections through the ferrules.

The ferrules ensure accurate mechanical alignment of fluid elements making accurate module placement easy.

It is generally easy to machine suitable ferrule recesses within the materials typically envisaged for use for baseboard and modules, giving scope for a range of ferrule and recess shapes. The internal bore and external diameter can be varied within limits, making it possible for the ferrule to incorporate microfluidic functionality. For example the internal bore could incorporate a

filtration function, optionally comprising multiple holes (in manner analogous to a photonic crystal). For example the ferrule can be modified to a larger shape to include a reservoir function.

Optionally the fluid coupling can incorporate additional functionality in that it includes within a fluid channel therewithin a fluidly active component, rather than serving merely as a channel. The fluid coupling could contain a non-return valve, for example a ball valve. The ball valve could conveniently be magnetically switchable valve. The fluid coupling could contain a catalyst frit or could incorporate a filter. Various switches could be conceived.

It is possible to use a conducting for example metallic fluid coupling such as a metallic ferrule to effect an electrical as well as a fluid interconnection between modules and/or boards. Such a metallic coupling may optionally be provided with an insulating layer on a fluid and/or module contacting surface, effecting an electrical contact between modules and/or electrical contact with fluid therein. A ferrule based design offers particular flexibility in that the system may readily be provided with further functional interconnections (eg magnetic, optical) either integral with or separately from the ferrule.

Optionally the ferrule can incorporate or be provided with a closure for closing a pathway not being used in a particular device combination allowing redundancy in pathway choice in base board for example during plug and play use. The closure may comprise a bung to be applied by a user, or an integral closure valve adapted to be operated manually, or to operate automatically on insertion of ferrule into recess.

The invention hereinabove has been described in terms of a single baseboard with a plurality of modules disposed in a single layer thereupon. It will be

readily appreciated that the invention is not so limited. A particular flexibility of the invention is that it allows for multi-level stacking of modules and/or primary base boards and/or intermediate level boards. Such intermediate level boards may serve merely to provide fluid connections in the form of channels, chambers or the like, or may also include active microfluidic components. Similarly, it will be understood that the invention encompasses modular structures comprising a plurality of modules as hereinbefore described and at least one primary base board, in which the base board is also optionally provided with active microfluidic components.

References hereinabove to features of the primary baseboard will be understood to be equally applicable to such intermediate level boards. Intermediate level boards may be constructed as above described and preferred features thereof will be construed by analogy. In particular, boards are preferably planar, and preferably of a sandwich construction as above.

In embodiments comprising such a multi-level stacking system, any component adapted for use at an intermediate level will comprise at least one inlet aperture on a first "lower" surface and at least one outlet aperture on a second "upper" surface (it being understood that lower and upper are being used herein as a convenience to refer to surfaces proximal and distal to the base board, and not to imply any restrictive orientation). References herein to inlets/outlets in a module will be understood to apply equally where appropriate to such a lower aperture, and references herein to a base board fluid supply aperture will be understood to apply equally where appropriate to such an upper aperture in an intermediate level component. It is particularly easy to stack multiple layers using the preferred ferrule embodiment.

In a preferred embodiment, fluid connections are effected by projecting ferrules between components adapted to lie generally parallel. In multi-level systems, it will be convenient that these ferrules all project in the same direction. In particular, ferrules are preferably provided at apertures in the upper surface of the base board and at apertures in the upper surface of all intermediate level modules, to be receivingly engaged in fluid tight connection within recessed portions at apertures on the lower surface of all intermediate level components and all top level components.

Attachment of a module to the board, or of an upper layer module, to a lower layer module in multi-layer systems, may be achieved by any suitable releasable attachment means, including without limitation screws or screw fixings, bayonet fittings whether quick release or not, push and snap fit connectors, vacuum or mechanical clamping connections, releasable mutually engageable resilient hook and felt pads, hooks, clips etc. The fluid couplings themselves, especially in the preferred form as channel means in interference fit between pairs of linked apertures, for example ferrules engaged in interference fit in recesses, may assist in or even suffice to constitute such mechanical connection. However, additional mechanical connectors will usually be preferred.

The system in accordance with the invention provides a plurality of interchangeable elements enabling a plurality of different microfluidic functions to be performed, on one or more levels.

In accordance with the invention in a further aspect a method of providing a microfluidic system as a modular assembly comprises assembling the system above described. In particular the method comprises the steps of:

providing at least one base board having a plurality of fluidly linked fluid supply apertures on one or both sides thereof and a plurality of fluid channels and/or chambers linking in fluid communication at least some of the supply apertures;

providing a plurality of microfluidic modules, each having one or more fluid inlets and/or outlets and at least one fluid channel or chamber in fluid communication therebetween;

connecting the modules to the base board via fluid couplings adapted to effect releasable fluid-tight connection therebetween via a supply aperture on the base board and an inlet/outlet on the module;

such that the fluid channels or chambers within the modules act in co-operation with fluid channels or chambers in the baseboard to complete a desired microfluidic circuit.

Other features of the method will be understood by analogy.

The invention will now be described by way of example only with reference to Figures 1 to 8 of the accompanying drawings wherein:

Figure 1 illustrates in cross section how fluid connection is effected between components in accordance with the invention;

Figure 2 is a schematic illustration of a simple basic construction of a microfluidic device for use with the invention;

Figure 3 is an example microreactor system employing the principles of the invention;

Figure 4 is a plan view of the baseboard of the reactor of Figure 3;

Figure 5 is an on chip manifold from the reactor of Figure 3;

Figure 6 is a plan view of a first active microfluidic device from the reactor of Figure 3;

Figure 7 is a plan view of a second active microfluidic device from the reactor of Figure 3;

Figure 8 is plan view of a third active microfluidic device from the reactor of Figure 3;

Figures 9 and 10 are examples of composite microfluidic device/ substrate arrangements using a combination of materials to achieve the best combination of properties;

Figures 11 and 12 are examples of reactor chip arrangements employing the composites of figures 9 and 10.

Figure 1 illustrates in cross section the basic design of fluid connection in accordance with the preferred embodiment of the invention employing projecting ferrules.

Illustrated schematically in Figure 1 are a baseboard (1), a first level component layer (2) and a second level component layer (3). The three layers are shown in exploded view disassembled but aligned for assembly.

Fluid connection within the system is effected by insertion of ferrules (7, 9) respectively provided at an upper supply aperture in the base board (1) and at an upper outlet aperture in the first level board (2) which are received in the recesses (6, 8) respectively provided in a lower surface of the first level board (2) and in a lower surface of the second level board (3). In the embodiment, the connection employs simple parallel-sided holes to take PTFE tubes forming the ferrules (7, 9) although it will be understood that more complex holes and ferrules are possible. The ferrules are retained within the holes in interference fit to provide a fluid tight leak proof connection.

In the example shown fluid supply is effected via an inlet fluid source aperture (10) comprising flexible tubing (11) of 1/16 inch (1.5 mm) diameter retained within HPLC fittings (12). The fluid path is shown by the dark line (14).

To assemble the modular structure into a laboratory system, a mechanical load is applied in the direction of the arrows (L) to effect engagement between the ferrules (7, 9) and the recesses (6, 8). Additional mechanical fixings (not shown) might be provided to ensure a more secure mechanical connection between the components (1, 2, 3).

A simple schematic device construction is illustrated in the exploded view in Figure 2. The example device has a sandwich layer structure comprising an external base layer (21) of polyetheretherketone (PEEK), a pair of inner layers (22) of photoimagable epoxy and an upper layer (24) of polymethylmethacrylate (PMMA) and internal layers (22). Channel means (23) are provided in the inner epoxy sandwich layer (22) to provide the necessary microfluidic microstructure.. Fluid ports (24) through the upper layer (24) give a fluid communication from a surface of the completed device to the channel means (23) which form enclosed internal channels once the two parts illustrated in the exploded view of Figure 2 are assembled.

The sandwich layer elements (22) and upper layer (24) contact fluid in use, respectively in the channels (23) and ports (25). Accordingly these are fabricated from materials exhibiting good chemical resistance, in the example respectively photimagable epoxy and PEEK. Properties of the merely structural lower layer (21) are less critical.

The simple schematic in Figure 2 does not illustrate any active microfluidic devices. It will be understood that these could be incorporated suitably within

the channels themselves (for example in particular if these take the form of pumps, valves, filters or the like) or could be incorporated on a module surface in fluid communication with the channels (23).

A microfluidic reaction system in accordance with the invention is illustrated in plan view in Figure 3. The reactor comprises inlets for two supply fluids ("fluid A" and "fluid B"), and provides for three processing streams ("stream 1", "stream 2", "stream 3").

The reactor comprises a baseboard (31) incorporating a plurality of fluid supply channels (32) therewithin. The base board has a number of microfluidic components mounted thereupon, being a manifold (34) to split the supply fluid (A, B) into the three streams (streams 1, 2, 3), and then within each stream a series of modules comprising a mixer chip (35), a detector chip (36), a reactor chip (37) and a further detector chip (36). These components are shown separately in Figures 4 to 8.

A system constructed in accordance with the principles of the invention as illustrated by figure 3 offers admirable simplicity and flexibility, providing a number of advantages over conventional designs. In particular it enables use of larger interconnect components and scaling from the macro to the micro world by microfluidic "fanning" (transition from large pitch to small pitch spacing between fluidic channels). Fittings from chip to board enable close packing of interconnections on <2 mm square packed spacing or <1 mm staggered spacing.

Figure 4 illustrates in plan view the baseboard (31) of Figure 3 without the components attached. The fluid channel means provided within the baseboard (32) are illustrated more clearly.

The manifold (34) of Figure 3 is illustrated in greater detail in plan view in Figure 5. It can be seen from Figure 5 how the manifold receives from a single inlet the two fluids (fluid A, fluid B) and produces 6 outlets, 1 to 6, effecting a paired supply of fluid A and fluid B to the three streams illustrated in Figure 3.

The device is constructed in accordance with the principles of Figure 2. Channel size in the example is 150 μm by 50 μm. Routing is effected through 300 μm channels. The overall size of the device is 62 by 72 by 4 mm.

Figure 6 illustrates in side view (above) and plan view (below) the micro mixer chip of Figure 3. The micromixer chip receives two fluid streams comprising fluid A and fluid B respectively in inlet A and inlet B. These are mixed together as they follow the flow channel (41) to the outlet. The chip is of a basic design as illustrated in Figure 2, with a channel size of 100 μm by 50 μm and an overall size of 45 by 25 by 4 mm. It is retained in position on the baseboard by means of the clamp (42).

Figure 7 is a representation of a reactor chip (37) from Figure 3 shown in side view (above) and plan view (below). Fluid flows from inlet to outlet via the flow channel (51) thereby passing through the reactor portion (53). The reactor portion comprises a catalyst bed (54) 3 mm in diameter and 2 mm deep retained by the screw in plug (55). The overall assembly has a channel size of 100 μm by 50 μm, an overall size of 36 by 25 by 6 mm, and is retained in position by the clamp (52).

Figure 8 illustrates the detector chip (36) of Figure 3 in side view (above) and plan view (below). Fluid flows from inlet to outlet via the flow channel (61).

The detector's active area (68) includes a light source in the form of an LED (63) or an optical fibre (not shown) to an external source, a diffraction grating (64) and a light collector in the form of the optical fibre (65). A lens (66) in front of the light source collimates the light and a lens (67) in front of the light collecting fibre improves the light collection efficiency. Collected light is sent for spectral analysis.

Additional electrical detection function is provided via groups of 3 gold microelectrodes (69), 110 µm wide on 200 µm pitch. Channel size is 400 µm by 400 µm, giving an overall device dimension of 50 x 30 x 5 mm.

It has been noted that systems in accordance with the invention can be given enhanced functionality by using a combination of materials and components and by using composite substrates for the baseboard and chips to achieve the best combination of properties.

For example, in the case of a microchemical reactor it is beneficial to use a "window" substrate polymer that is transparent to enable easy inspection of the fluid path, but in which inserts are included in the substrate in the regions where solvent contact is possible; preventing contact with the "window" substrate.

An example of such a composite structure is given in figure 9. In the figure different materials are represented by different shading, comprising, in accordance with the illustrated key:

71 - Baseboard substrate material (e.g. PMMA);

72 - Chip substrate material (e.g. PMMA)

73 - photoimagable epoxy

74 - Chemically resistant inserts (e.g. PEEK)

75 - Ferrules (e.g. PTFE)

76 - Fluid connector (e.g. PEEK)

The insert is simply a cylinder traversing the substrate through which is drilled a fluid path way and recess to support a ferrule. The material of the insert can be chosen from high chemical resistance polymers such as PEEK or PTFE or in a curable resin formed by micromoulding or lithographically using a photoformable resin. The inserts can be produced by any method including machining or injection moulding.

More complex inserts might have the ferrule integral with the insert. Although this would inhibit ferrule replacement it may be a good option for large arrays of chips where multiple ferrule insertion would be time consuming. This is illustrated by the elements 77 in figure 10, where otherwise like numerals are used for like materials.

The concept of using a composite approach to achieve the required properties at the optimum location can also be extended to the microfluidic channel walls. The surface properties of the walls should ideally be matched to the desired flow characteristics of the material being transported by the channel. For example, if low wall contact resistance is required a low surface energy coating is a more convenient method of achieving the desired effect compared to producing the whole system in a low surface energy polymer. For example, a photoimagable epoxy treated with Fluorolink S10 (Ausimont) - a di-triethoxysilane based on a linear perfluoropolyether backbone reduces the surface energy to 13 dynes/cm. Conveniently the walls of the channels can alternatively be treated to make them hydrophilic or hydrophobic or to provide biocompatibility etc.

A further benefit of the interconnected baseboard and processor chip concept underlying the present invention is the possibility of application to scale up by scale out. Scale out is the term often applied to increasing output from a processor chip performing, for example, a synthetic procedure by multiplying the number of processor chips. This preserves the reaction conditions for the channel dimensions optimised for a single process or series of processes which would otherwise change if the channel dimensions were increased to achieve higher throughput. This can be achieved by the baseboard functioning as a manifold, supplying reagents to an array of processor chips. The manifold can provide a single sided input to multiple outputs from each processor chip). A manifold on one side can provide an interdigitated input and output array of channels or one side can provide an input manifold and a higher level board can provide an output manifold.

Examples of such arrangements exploiting the composite concept are shown in figures 11 and 12, respectively illustrating the use of a baseboard as a manifold for supplying fluid in parallel to an array of processors with multiple outputs from each processor chip and the use of baseboards as input and output manifolds for feeding processor chips in parallel for scale up by scale out or by processor replication. The shading key of Figures 9 and 10 is applied to the systems illustrated in figures 11 and 12.

The interconnection system provides a ready means of developing processes by series interconnection of each operation with optimisation of each operation readily achieved by exchange of chips. Once a series of operations are optimised they can be conveniently integrated into a single chip and then if required converted into arrays with the baseboard providing multiple feeds for use in high throughput screening or the baseboard serving as input and output manifolds for process replication to scale up or achieve increased throughput

by scale out. In this way very large numbers of chips can be arrayed to achieve a production capability.

The complete system can be a complete hybrid of materials with for example the baseboard manifold being in polymer, the ferrule seals in polymer, the processor chips in glass, the pumping and valving system in metal possibly with internal polymer seals etc.

CLAIMS

1. A modular microfluidic system comprising at least one base board having a plurality of fluidly linked fluid supply apertures on one or both sides thereof, a plurality of microfluidic modules adapted to be detachably attached to the base board, each having one or more fluid inlets and/or outlets, and a plurality of fluid couplings to effect releasable fluid-tight connection between a module and a base board via a supply aperture on the base board and an inlet/outlet on the module.

2. A modular microfluidic system in accordance with claim 1 further comprising at least one fluid source aperture fluidly linked thereto to supply source fluid to the system, and/or at least one fluid output aperture fluidly linked thereto to output fluid from the system.

3. A modular microfluidic system in accordance with claim 1 or claim 2 wherein the base board is constructed with a pattern of interconnecting microfluidic channels to provide a plurality of fluid channels and/or chambers in use linking in fluid communication at least some of the supply apertures to each other and/or to the source aperture.

4. A modular microfluidic system in accordance with any preceding claim wherein each microfluidic module comprises one or more microfluidic devices.

5. A modular microfluidic system in accordance with claim 4 wherein the microfluidic devices include devices selected from the list comprising a reactor, heater, cooler, analyser, detector, mixer, processor, separator or

the like, a pump, valve, filter or the like, or a fluid channel, chamber or manifold.

6. A modular microfluidic system in accordance with any preceding claim wherein each module has a generally planar construction to be incorporated upon a generally planar baseboard.

7. A modular microfluidic system in accordance with any preceding claim wherein different parts of boards and/or modules are fabricated from different materials to provide different functional requirements regarding transparency, structural strength, chemical resistance and the like.

8. A modular microfluidic system in accordance with claim 7 wherein a board and/or module comprises a composite structure having areas of a transparent material where required, and areas of a chemically resistant material at least in regions where solvent contact is possible, preventing contact with the less resistant transparent substrate material.

9. A modular microfluidic system in accordance with any preceding claim wherein connecting means are provided to hold the assembly together in use and assist in maintenance of a fluid-tight connection by urging coupling and aperture into closer association and retaining thereat with a suitable urging force.

10. A modular microfluidic system in accordance with any preceding claim wherein a plurality of releasable fluid couplings are provided to effect a fluid-tight connection between at least one fluid supply aperture on a base board and at least one inlet/outlet on a microfluidic device module.

11. A modular microfluidic system in accordance with claim 10 wherein the releasable coupling is in the form of a channel means removably insertable into a suitable recess in such a inlet/outlet/aperture to effect a fluid tight communicating connection therebetween.

12. A modular microfluidic system in accordance with claim 11 wherein the channel means comprises a rigid tubular element, with any recess into which such a tubular element is to be received being shaped accordingly.

13. A modular microfluidic system in accordance with claim 12 wherein the tubular element comprises a projecting ferrule integral with and projecting from a first aperture comprising either a fluid supply aperture in the base board or an inlet/outlet in the module, and adapted to be received in a recess comprised as a second aperture, correspondingly either an inlet/outlet in the module or a supply aperture in the base board.

14. A modular microfluidic system in accordance with claim 13 wherein the ferrule projects generally perpendicularly from a generally planar surface of the base board, to effect a fluid connection between a base board and module adapted to lie generally parallel when connected.

15. A modular microfluidic system in accordance with one of claims 10 to 14 wherein the removably insertable channel means incorporates or is provided with a closure for closing a pathway not being used in a particular device combination.

16. A modular microfluidic system in accordance with any preceding claim wherein the fluid coupling includes within a fluid channel therewithin a fluidly active component

17. A modular microfluidic system in accordance with any preceding claim wherein the fluid coupling is metallic fluid coupling such as a metallic ferrule to effect an electrical as well as a fluid interconnection.

18. A modular microfluidic system in accordance with any preceding claim, comprising a plurality of modules, a base board and one or more intermediate level board constructed in like manner to the base board, the assembly being adapted for multi-level stacking of modules and/or base boards and/or intermediate level boards.

19. A modular microfluidic system in accordance with claim 18 wherein channel means comprising rigid tubular ferrules are provided at apertures in the upper surface of the base board and at apertures in the upper surface of all intermediate level modules, to be receivingly engaged in fluid tight connection within recessed portions at apertures on the lower surface of all intermediate level components and all top level components.

20. A method of providing a microfluidic system as a modular assembly comprising the steps of:
providing at least one base board having a plurality of fluidly linked fluid supply apertures on one or both sides thereof and a plurality of fluid channels and/or chambers linking in fluid communication at least some of the supply apertures;
providing a plurality of microfluidic modules, each having one or more fluid inlets and/or outlets and at least one fluid channel or chamber in fluid communication therebetween;

connecting the modules to the base board via fluid couplings adapted to effect releasable fluid-tight connection therebetween via a supply aperture on the base board and an inlet/outlet on the module;
such that the fluid channels or chambers within the modules act in co-operation with fluid channels or chambers in the baseboard to complete a desired microfluidic circuit.

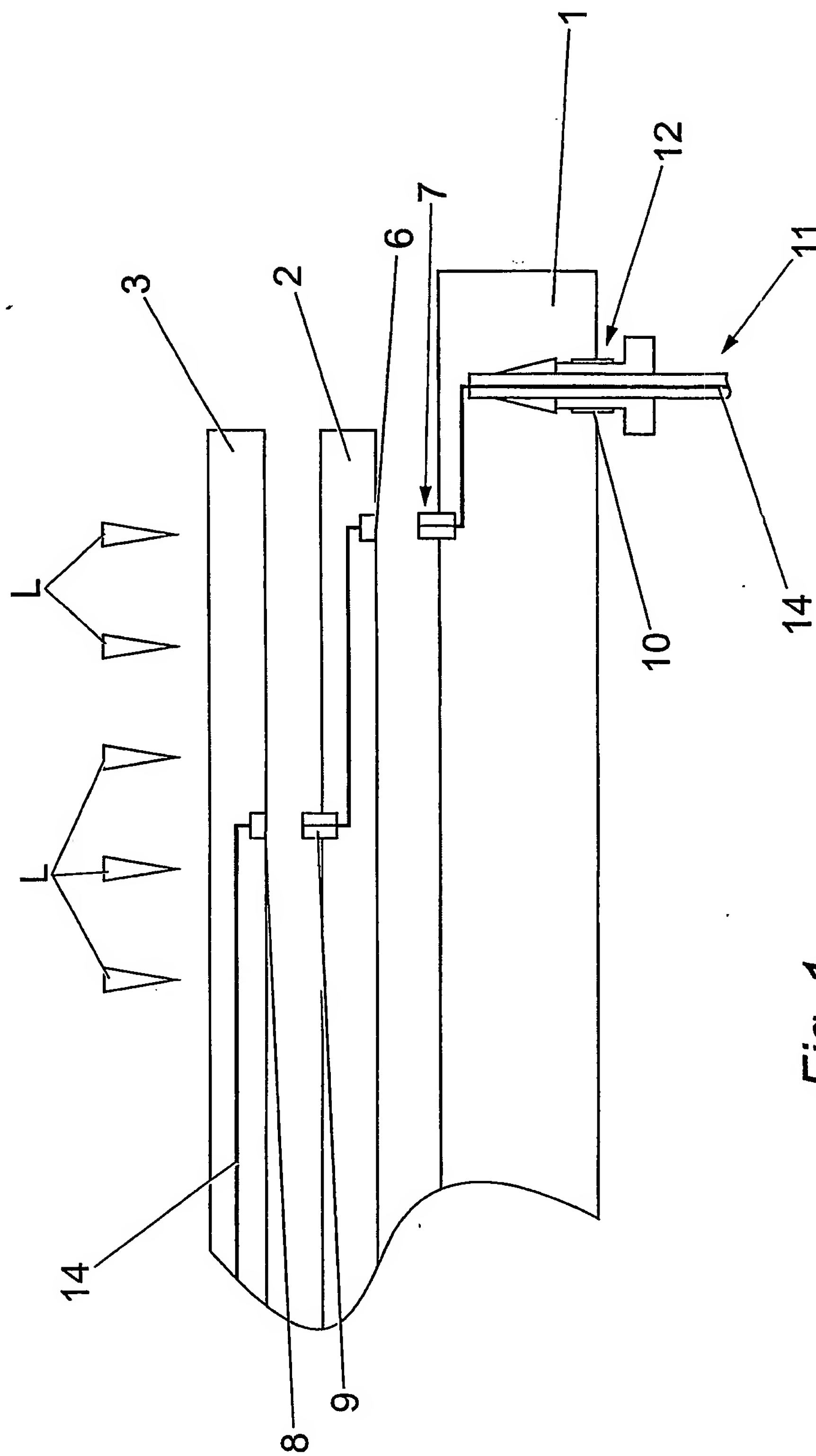


Fig. 1

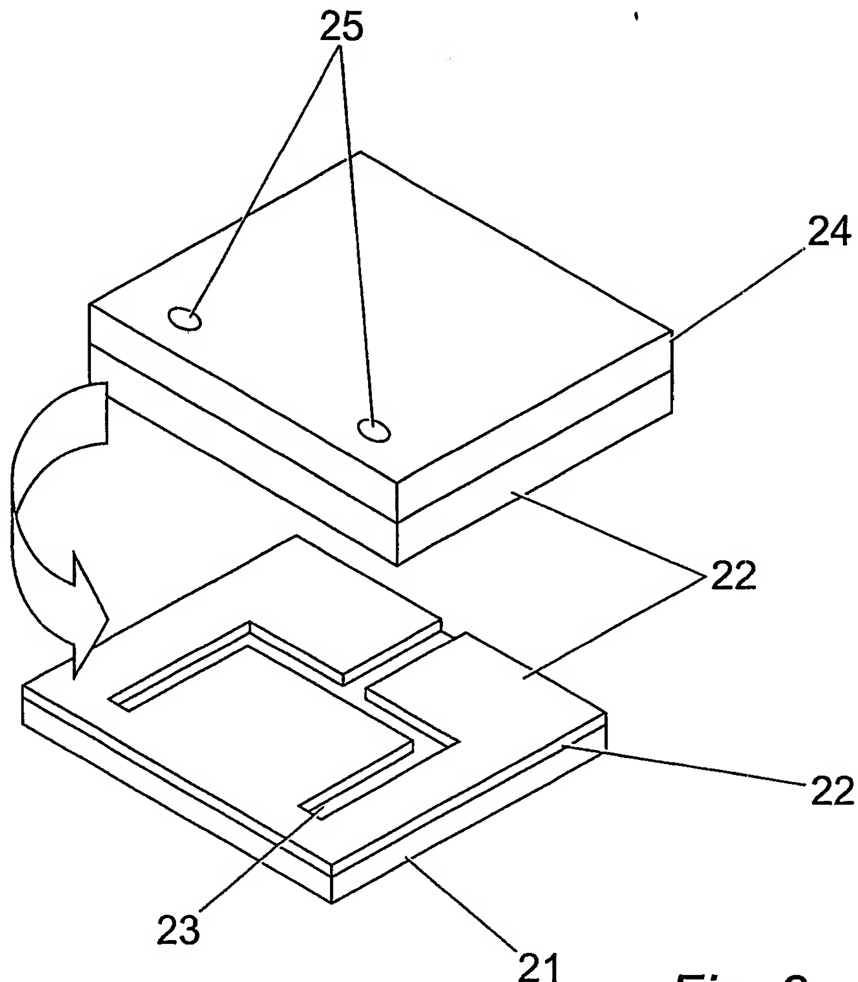


Fig. 2

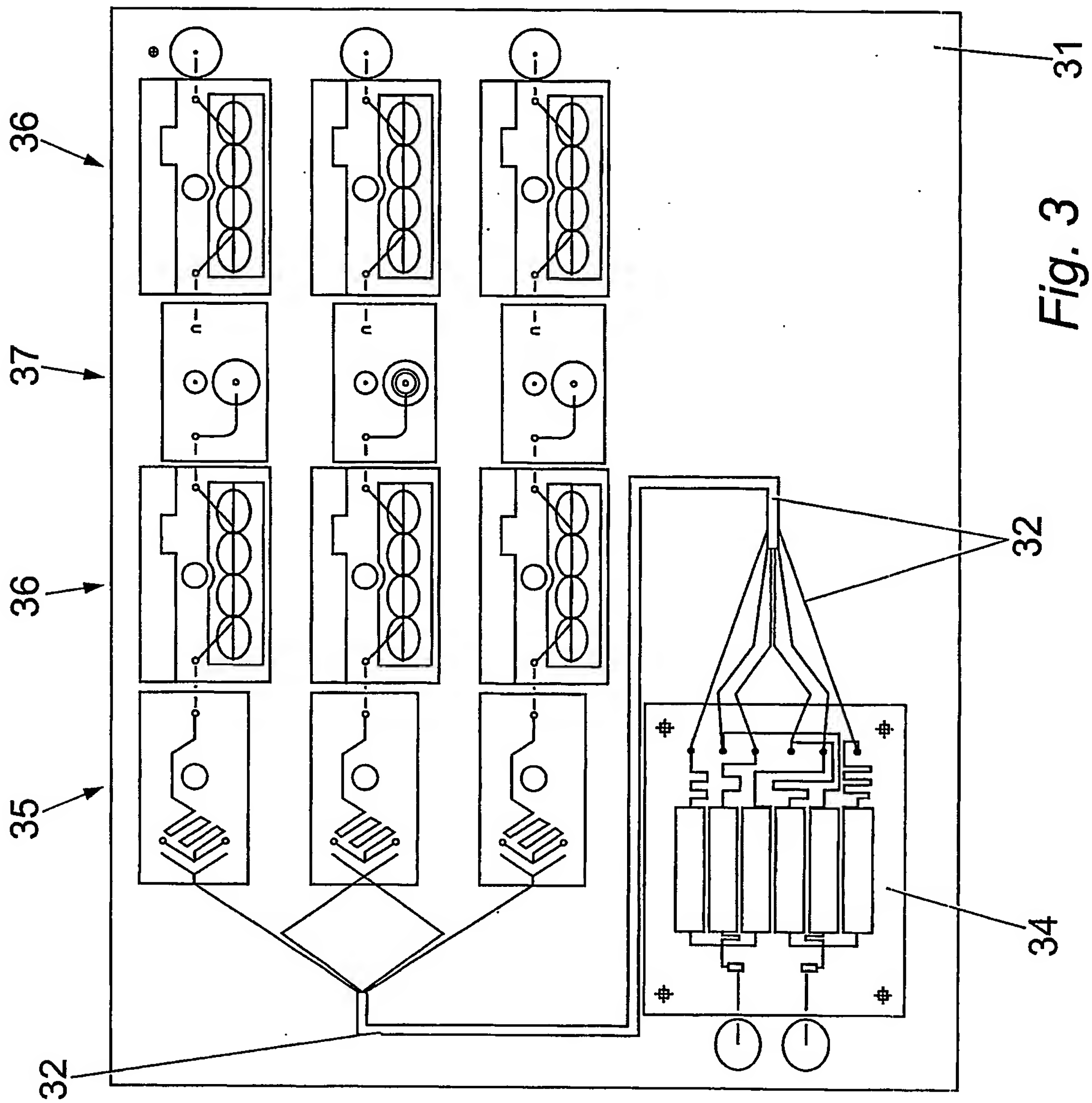


Fig. 3

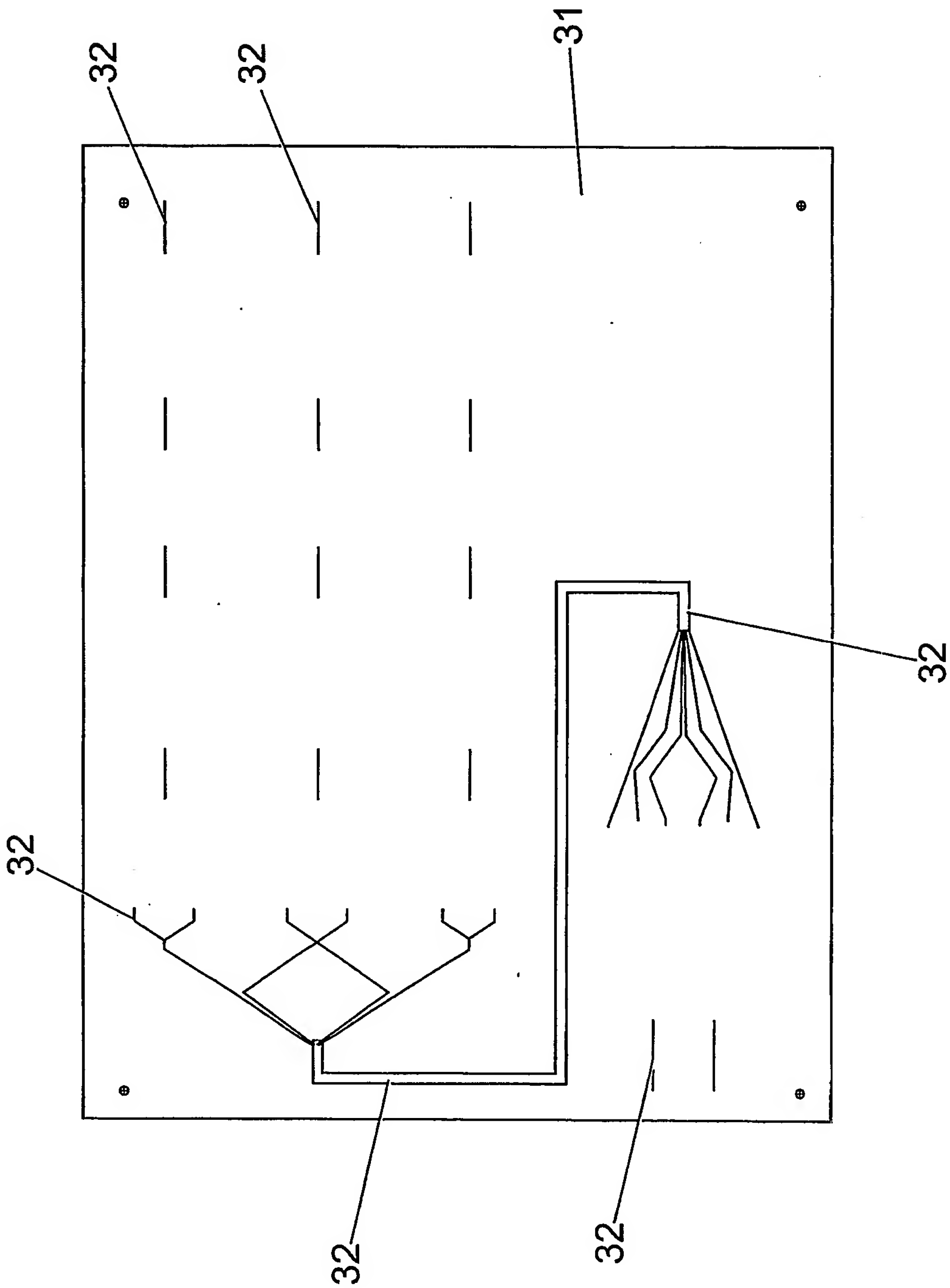


Fig. 4

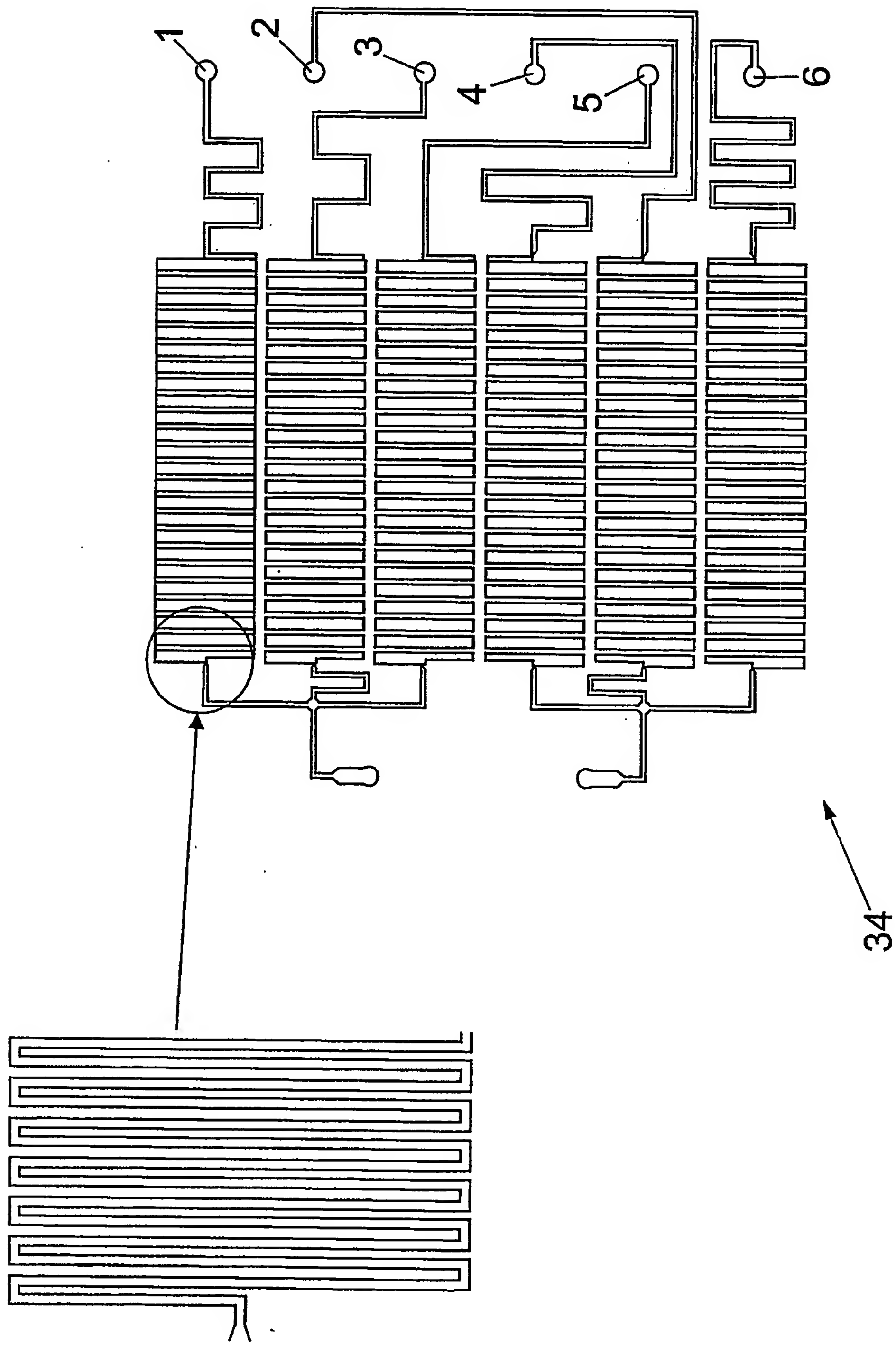


Fig. 5

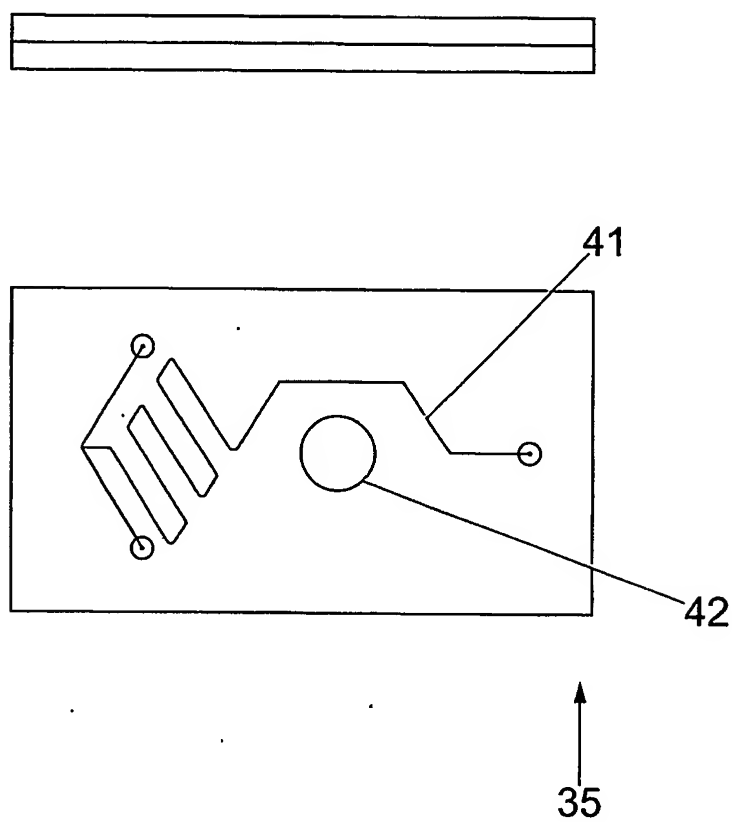


Fig. 6

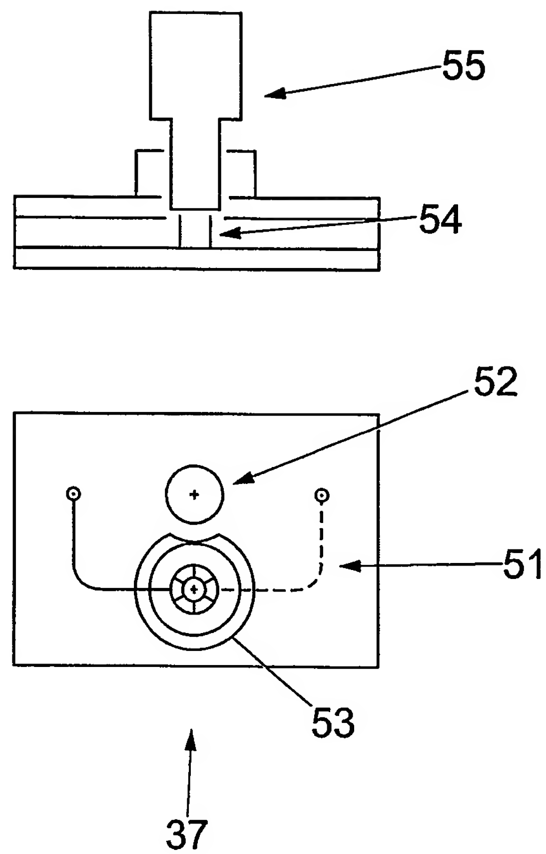


Fig. 7

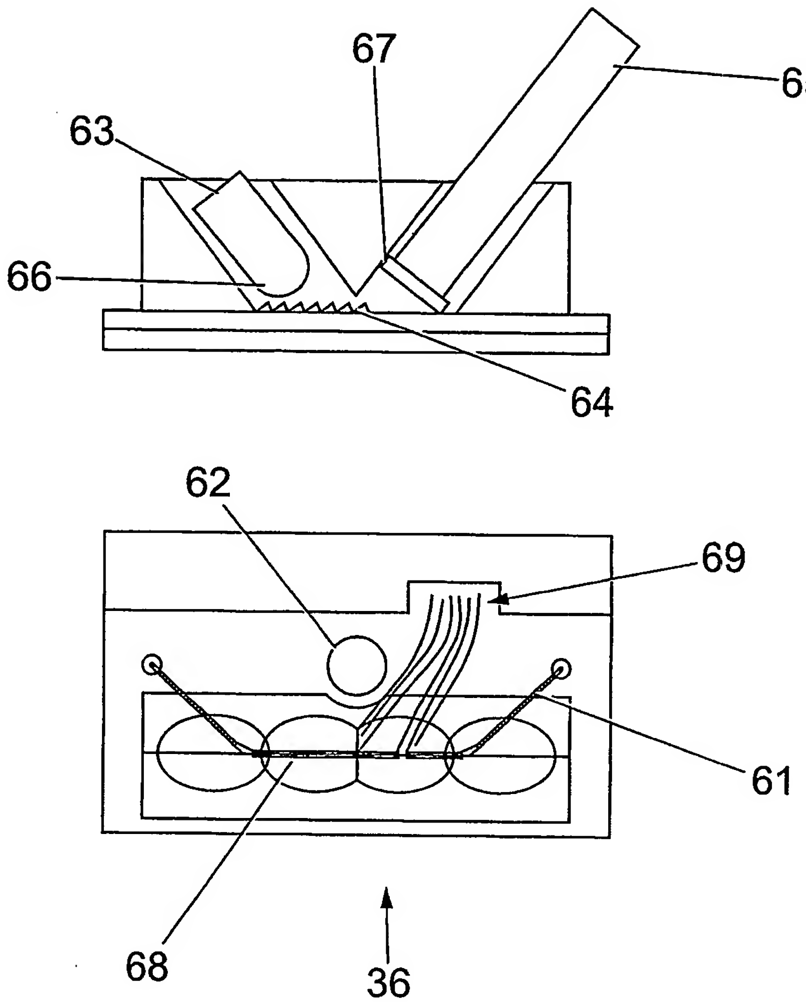


Fig. 8

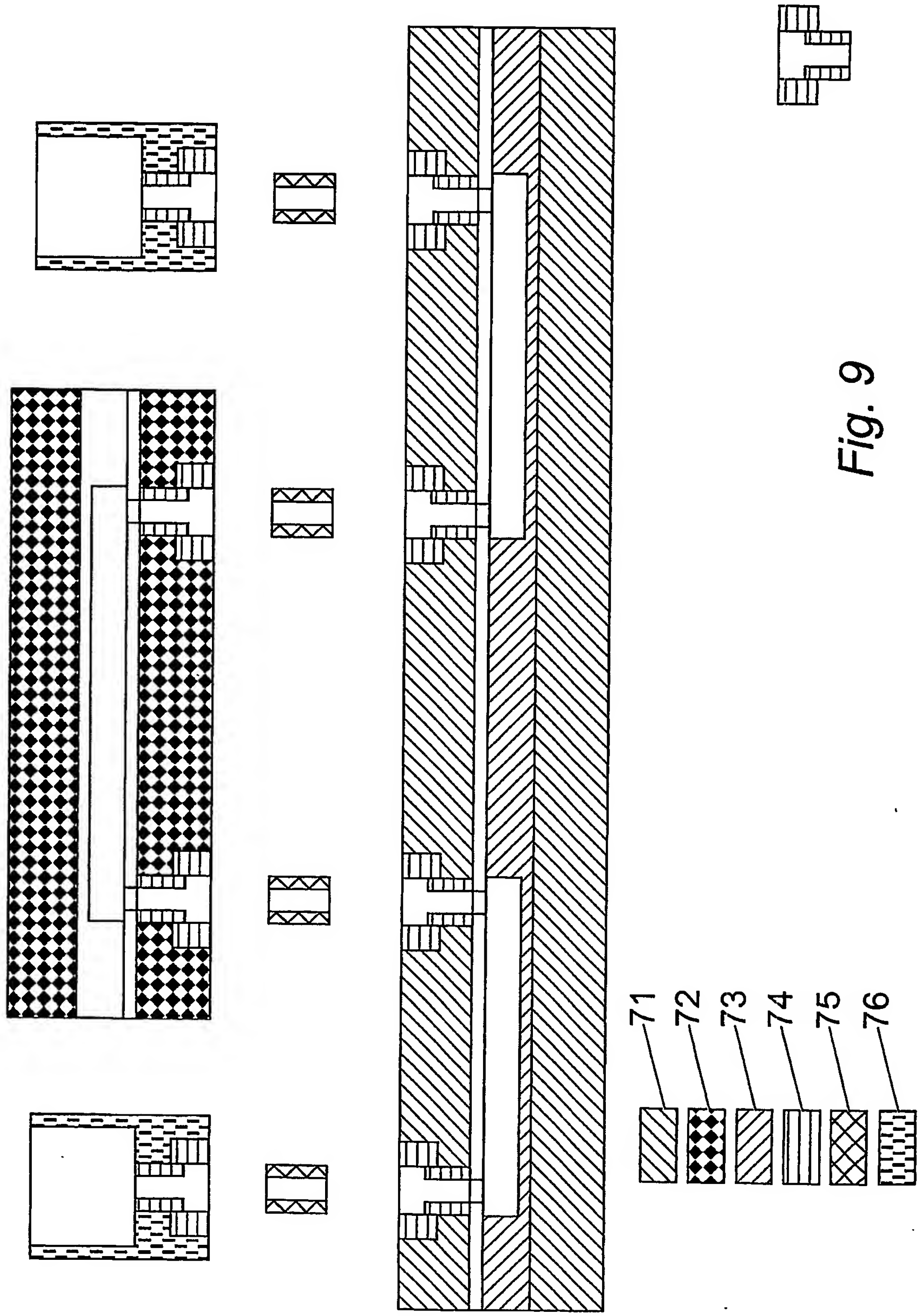


Fig. 9

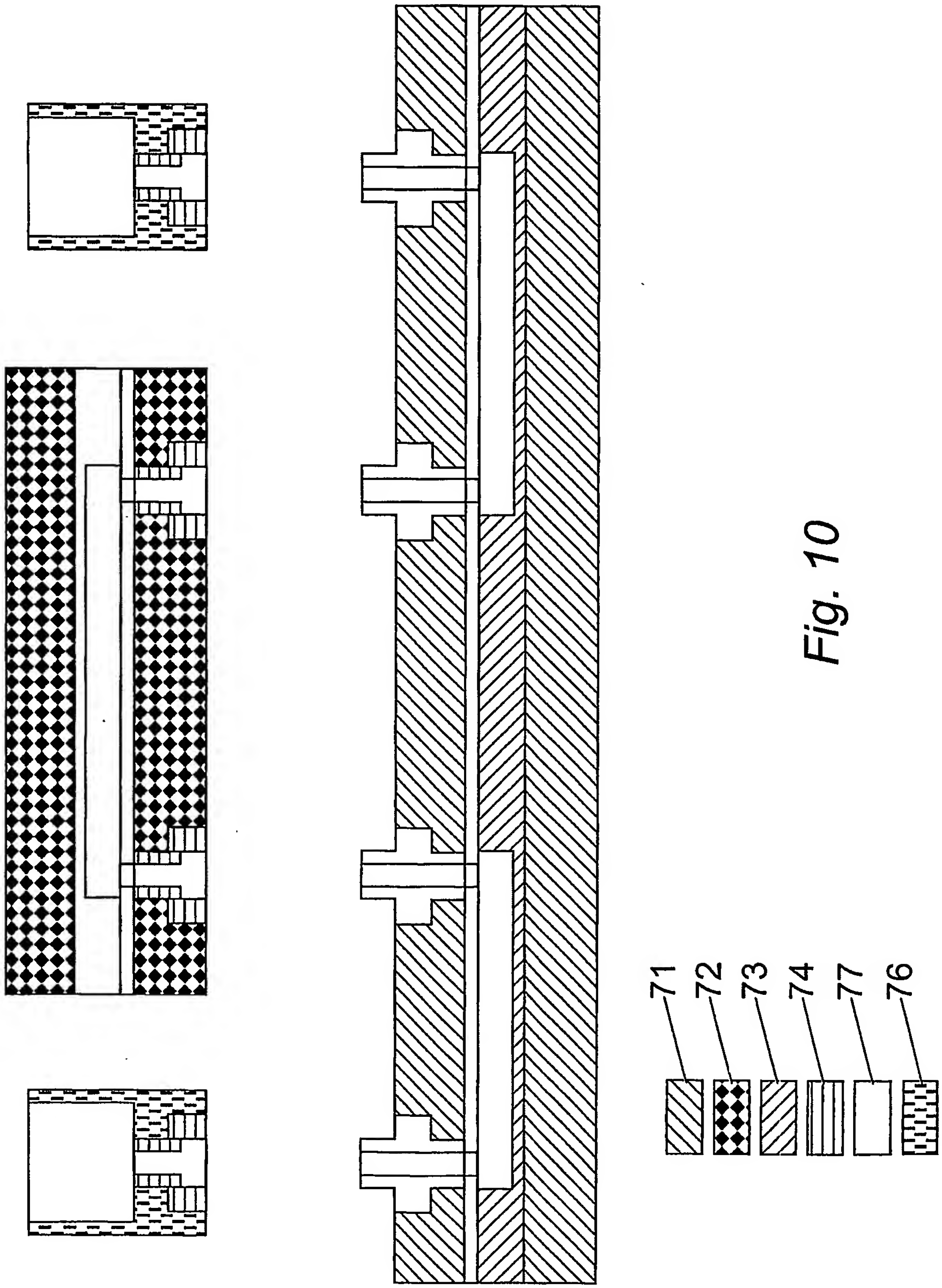


Fig. 10

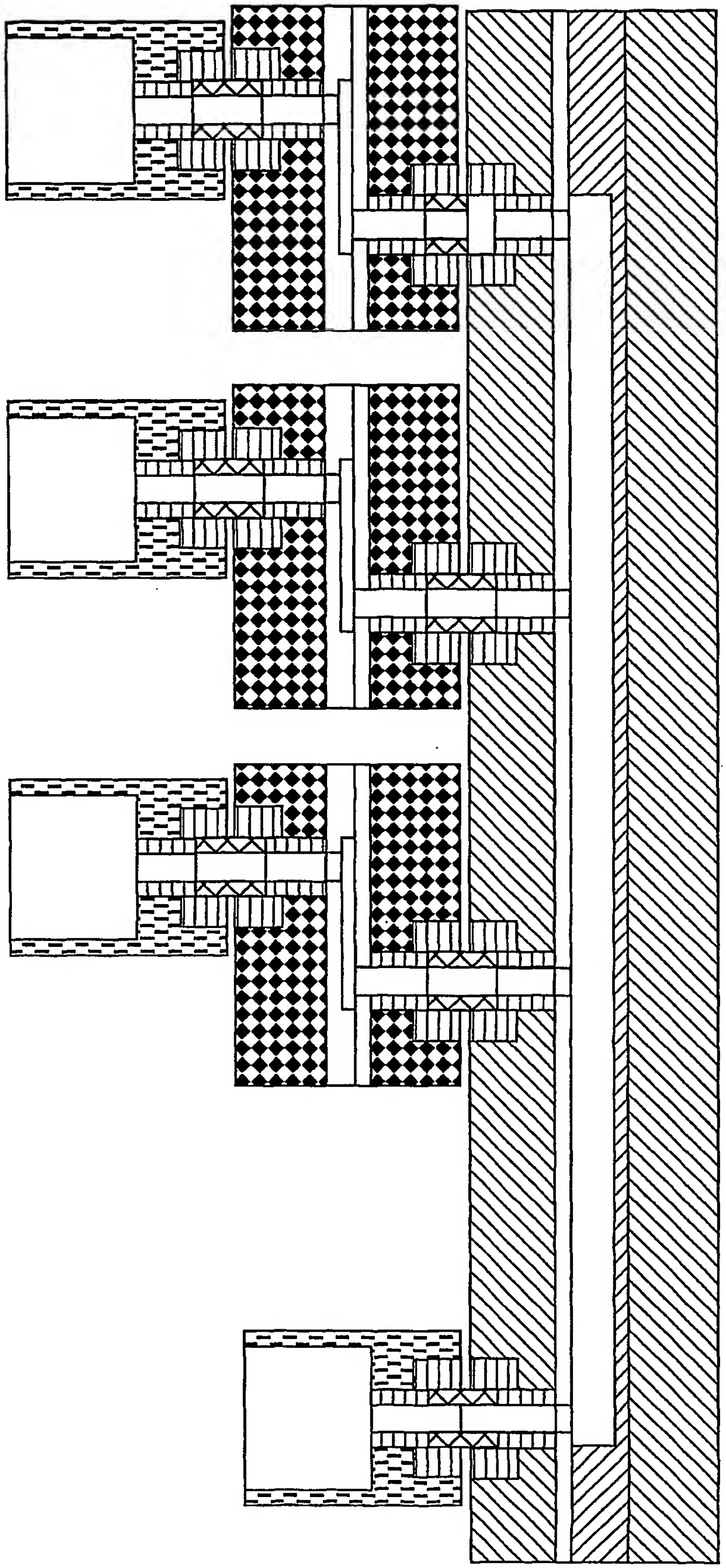


Fig. 11

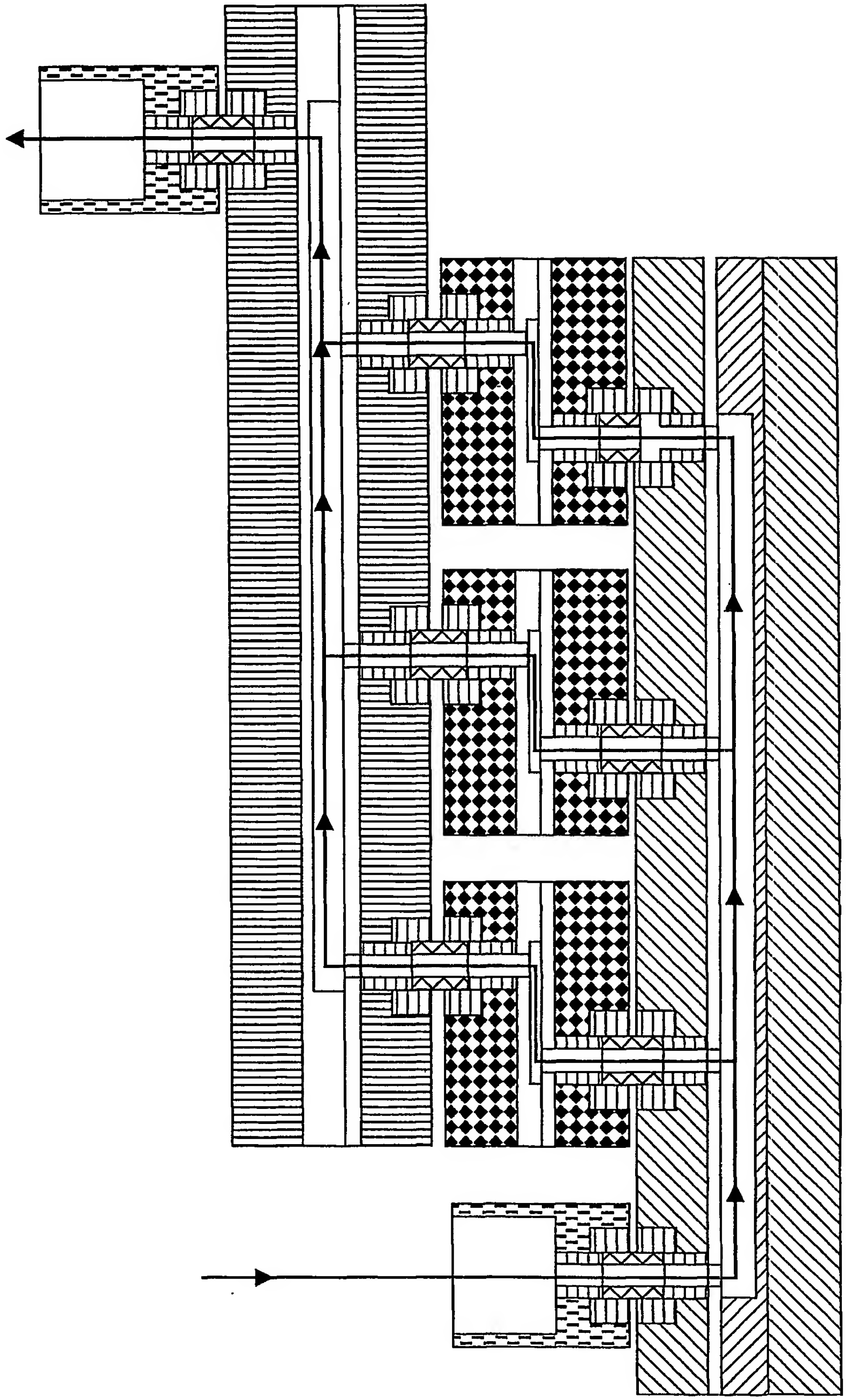


Fig. 12

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/03853

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01L3/00 B81B1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01L B81B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 02 30560 A (PEZZUTO MARCI ;DANTSKER EUGENE (US); NANOSTREAM INC (US); CONNOR S) 18 April 2002 (2002-04-18) paragraph '0051! - paragraph '0056!	1-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 December 2003	16/12/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Tragoustis, M

INTERNATIONAL SEARCH REPORT

Internatio ›lication No
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